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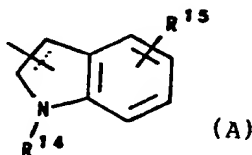
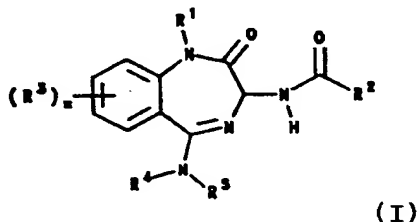
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<p>(21) International Application Number: PCT/GB93/01599</p> <p>(22) International Filing Date: 28 July 1993 (28.07.93)</p> <p>(30) Priority data:</p> <table border="0"> <tr><td>9216123.1</td><td>29 July 1992 (29.07.92)</td><td>GB</td></tr> <tr><td>9216238.7</td><td>30 July 1992 (30.07.92)</td><td>GB</td></tr> <tr><td>9216231.2</td><td>30 July 1992 (30.07.92)</td><td>GB</td></tr> <tr><td>9220957.6</td><td>6 October 1992 (06.10.92)</td><td>GB</td></tr> <tr><td>9222821.2</td><td>30 October 1992 (30.10.92)</td><td>GB</td></tr> <tr><td>9222934.3</td><td>2 November 1992 (02.11.92)</td><td>GB</td></tr> <tr><td>9223583.7</td><td>11 November 1992 (11.11.92)</td><td>GB</td></tr> <tr><td>9226242.7</td><td>16 December 1992 (16.12.92)</td><td>GB</td></tr> <tr><td>9226360.7</td><td>17 December 1992 (17.12.92)</td><td>GB</td></tr> <tr><td>9301277.1</td><td>22 January 1993 (22.01.93)</td><td>GB</td></tr> <tr><td>9307318.7</td><td>7 April 1993 (07.04.93)</td><td>GB</td></tr> </table> <p>(71) Applicant (for all designated States except US): MERCK SHARP &amp; DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): CASTRO PINEIRO, Jose, Luis [ES/GB]; 92 The Hornbeams, Harlow, Essex CM20 1PQ (GB). CARLING, William, Robert [GB/GB]; 15 The Colts, Thorley Park, Bishops Stortford, Hertfordshire CM23 4DL (GB). CHAMBERS, Mark,</p>		9216123.1	29 July 1992 (29.07.92)	GB	9216238.7	30 July 1992 (30.07.92)	GB	9216231.2	30 July 1992 (30.07.92)	GB	9220957.6	6 October 1992 (06.10.92)	GB	9222821.2	30 October 1992 (30.10.92)	GB	9222934.3	2 November 1992 (02.11.92)	GB	9223583.7	11 November 1992 (11.11.92)	GB	9226242.7	16 December 1992 (16.12.92)	GB	9226360.7	17 December 1992 (17.12.92)	GB	9301277.1	22 January 1993 (22.01.93)	GB	9307318.7	7 April 1993 (07.04.93)	GB	<p>Stuart [GB/GB]; 10 Park Avenue Maisonettes, North Bushey, Watford, Hertfordshire WD2 2BR (GB). FLETCHER, Stephen, Robert [GB/GB]; 10 Clipped Hedge, Hatfield Heath, Nr. Bishops Stortford, Hertfordshire CM22 7EG (GB). HOBBS, Sarah, Christine [GB/GB]; 27 Goodwin Stile, Thorley Park, Bishops Stortford, Hertfordshire CM23 4EP (GB). MATASSA, Victor, Giulio [GB/GB]; The Duck Street Barns, Furneux Pelham, Hertfordshire SG9 0LA (GB). MOORE, Kevin, William [GB/GB]; 22 White Hart Close, Buntingford, Hertfordshire SG9 9DG (GB). SHOWELL, Graham, Andrew [GB/GB]; 5 Beehive Lane, Welwyn Garden City, Hertfordshire AL7 4BB (GB). RUSSEL, Michael, Geoffrey, Neil [GB/GB]; 11 Stapleford, Panshanger, Welwyn Garden City, Hertfordshire AL7 2PD (GB).</p> <p>(74) Agent: QUILLIN, Helen, Kaye; Merck &amp; Co., Inc., European Patent Department, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).</p> <p>(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>	
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(54) Title: BENZODIAZEPINE DERIVATIVES



(57) Abstract

Compounds of formula (I), and salts and prodrugs thereof, wherein R<sup>1</sup> represents H, optionally substituted C<sub>1-6</sub>alkyl or C<sub>3-7</sub>cycloalkyl; R<sup>2</sup> is NHR<sup>12</sup> or (CH<sub>2</sub>)<sub>s</sub>R<sup>13</sup> where s is 0, 1 or 2; R<sup>3</sup> represents C<sub>1-6</sub>alkyl, halo or NR<sup>6</sup>R<sup>7</sup>; R<sup>4</sup> and R<sup>5</sup> are H, C<sub>1-12</sub>alkyl optionally substituted by NR<sup>9</sup>R<sup>9'</sup> or an azacyclic or azabicyclic group, optionally substituted C<sub>4-9</sub>cycloalkyl, C<sub>4-9</sub>cycloalkylC<sub>1-4</sub>alkyl, aryl, arylC<sub>1-6</sub>alkyl or azacyclic or azabicyclic groups, or R<sup>4</sup> and R<sup>5</sup> together form the residue of an optionally substituted azacyclic or azabicyclic ring system; x is 0, 1, 2 or 3; R<sup>12</sup> is optionally substituted phenyl or pyridyl; R<sup>13</sup> represents a group (A) wherein R<sup>14</sup> is H or C<sub>1-6</sub>alkyl; R<sup>15</sup> is H, C<sub>1-6</sub>alkyl, halo or NR<sup>6</sup>R<sup>7</sup>; and the dotted line is an optional covalent bond; are CCK and/or gastrin antagonists useful in therapy.

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## BENZODIAZEPINE DERIVATIVES

5 This invention relates to benzodiazepine compounds which are useful as antagonists of cholecystokinin and gastrin receptors.

Cholecystokinins (CCK) and gastrin are structurally related peptides which exist in gastrointestinal tissue and in the central nervous system (see, V. Mutt, Gastrointestinal Hormones, G.B.J. Green, Ed., Raven Press, N.Y., p.169 and G. Nission, ibid. p.127).

Cholecystokinins include CCK-33, a neuropeptide of thirty-three amino acids in its originally isolated form (see, Mutt and Jorpes, Biochem. J. 125, 678 (1971)), its carboxylterminal octapeptide, CCK-8 (also a naturally-occurring neuropeptide and the minimum fully active sequence), and 39- and 12-amino acid forms. Gastrin occurs in 34-, 17- and 14-amino acid forms, with the minimum active sequence being the C-terminal tetrapeptide, Trp-Met-Asp-Phe-NH<sub>2</sub>, which is the common structural element shared by both CCK and gastrin.

CCKs are believed to be physiological satiety hormones, thereby possibly playing an important role in appetite regulation (G. P. Smith, Eating and Its Disorders, A. J. Stunkard and E. Stellar, Eds, Raven Press, New York, 1984, p. 67), as well as stimulating colonic motility, gall bladder contraction, pancreatic enzyme secretion and inhibiting gastric emptying. They reportedly co-exist with dopamine in certain mid-brain neurons and thus may also play a role in the functioning of dopaminergic systems in the brain, in addition to serving as neurotransmitters in their own right (see A. J. Prange et al., "Peptides in the Central Nervous

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System", Ann. Repts. Med. Chem 17, 31, 33 [1982] and references cited therein; J. A. Williams, Biomed Res. 3 107 [1982]; and J.E. Morley, Life Sci. 30, 479 [1982]).

5 The primary role of gastrin, on the other hand, appears to be stimulation of the secretion of water and electrolytes from the stomach and, as such, is involved in control of gastric acid and pepsin secretion. Other physiological effects of gastrin then include increased mucosal blood flow and increased antral motility. Rat  
10 studies have shown that gastrin has a positive trophic effect on the gastric mucosa, as evidenced by increased DNA, RNA and protein synthesis.

There are at least two subtypes of cholecystokinin receptors termed CCK-A and CCK-B (T.H. Moran et al., "Two brain cholecystokinin receptors: implications for behavioural actions", Brain Res., 362, 175-79 [1986]). Both subtypes are found both in the  
15 periphery and in the central nervous system.

CCK and gastrin receptor antagonists have been disclosed for preventing and treating CCK-related and/or  
20 gastrin related disorders of the gastrointestinal (GI) and central nervous (CNS) systems of animals, especially mammals, and more especially those of humans. Just as there is some overlap in the biological activities of CCK  
25 and gastrin, antagonists also tend to have affinity for both CCK-B receptors and gastrin receptors. Other antagonists have activity at the CCK-A subtype.

Selective CCK antagonists are themselves useful in treating CCK-related disorders of appetite regulatory  
30 systems of animals as well as in potentiating and prolonging opiate-mediated analgesia [see P. L. Faris et al., Science 226, 1215 (1984)], thus having utility in the treatment of pain. CCK-B and CCK-A antagonists have also been shown to have a direct analgesic effect [M.F.



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O'Neill et al., Brain Research, 534 287 (1990)].

Selective CCK and gastrin antagonists are useful in the modulation of behaviour mediated by dopaminergic and serotonergic neuronal systems and thus have utility in the treatment of schizophrenia and depression (Rasmussen et al., 1991, Eur. J. Pharmacol., 209, 135-138; Woodruff et al., 1991, Neuropeptides, 19, 45-46; Cervo et al., 1988, Eur. J. Pharmacol., 158, 53-59), as a palliative for gastrointestinal neoplasms, and in the treatment and prevention of gastrin-related disorders of the gastrointestinal system in humans and animals, such as peptic ulcers, Zollinger-Ellison syndrome, antral G cell hyperplasia and other conditions in which reduced gastrin activity is of therapeutic value, see e.g. U.S. Patent 4,820,834. Certain CCK antagonists are useful anxiolytic agents and can be used in the treatment of panic and anxiety disorders.

CCK has been reported to evoke the release of stress hormones such as adrenocorticotrophic hormone,  $\beta$ -endorphin, vasopressin and oxytocin, CCK may function as a mediator of responses to stress and as part of the arousal system. CCK-A receptors are now known to be present in a number of areas of the CNS and may be involved in modulating all of the above.

CCK may be involved in the regulation of stress and its relationship with drug abuse e.g. alleviation of the benzodiazepine withdrawal syndrome (Singh et al., 1992, Br. J. Pharmacol., 105, 8-10) and neuroadaptive processes.

Since CCK and gastrin also have trophic effects on certain tumours [K. Okyama, Hokkaido J. Med. Sci., 206-216 (1985)], antagonists of CCK and gastrin are useful in treating these tumours [see, R.D. Beauchamp et al., Ann. Surg., 202, 203 (1985)].

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In the light of discussion in C. Xu et al., Peptides, 8, 1987, 769-772, CCK antagonists may also be effective in neuroprotection.

CCK receptor antagonists have been found to  
5 inhibit the contractile effects of CCK on iris sphincter and ciliary muscles of monkey and human eyes (Eur. J. Pharmacol., 211(2), 183-187; A. Bill et al., Acta Physiol. Scand., 138, 479-485 [1990]), thus having utility in inducing miosis for therapeutic purposes.

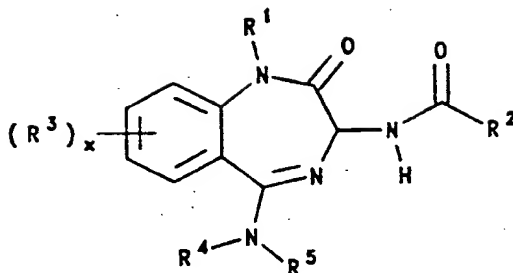
10 A class of benzodiazepine antagonist compounds has been reported which binds selectively to brain CCK (CCK-B and CCK-A) and gastrin receptors [see M. Bock et al., J. Med Chem., 32, 13-16 (1989)].

15 European patent application no. 0 167 919 discloses benzodiazepine CCK and gastrin antagonists substituted in the 3-position by, inter alia, a phenyl urea or an indole amide and at the 5-position by an optionally substituted phenyl or pyridyl group.

20 United States Patent no. 3,414,563 discloses benzodiazepine derivatives optionally substituted at the 3-position by C<sub>1-4</sub>alkyl or phenyl and substituted at the 5-position by an amino, alkylamino or dialkylamino group or a 3 to 8-membered azacycle, bound through nitrogen, which azacycle may optionally contain a further O, S or N  
25 atom. The compounds are said to have CNS activity. There is no suggestion of a nitrogen-containing substituent at the 3-position. Nor is there any suggestion that the disclosed compounds are antagonists at CCK or gastrin receptors.

30 The present invention provides benzodiazepine compounds of formula (I):

- 5 -



(I)

wherein:

$R^1$  represents H,  $C_{1-6}$ alkyl optionally substituted by one or more halo,  $C_{3-7}$ cycloalkyl, cyclopropylmethyl,  $(CH_2)_r$ imidazolyl,  $(CH_2)_r$ triazolyl,  $(CH_2)_r$ tetrazolyl (where  $r$  is 1, 2 or 3),  $CH_2CO_2R^{11}$  (where  $R^{11}$  is  $C_{1-4}$ alkyl) or  $CH_2CONR^6R^7$  (where  $R^6$  and  $R^7$  each independently represents H or  $C_{1-4}$ alkyl, or  $R^6$  and  $R^7$  together form a chain  $(CH_2)_p$  where  $p$  is 4 or 5);

$R^2$  represents  $NHR^{12}$  or  $(CH_2)_sR^{13}$  where  $s$  is 0, 1 or 2;

$R^3$  represents  $C_{1-6}$ alkyl, halo or  $NR^6R^7$ , where  $R^6$  and  $R^7$  are as previously defined;

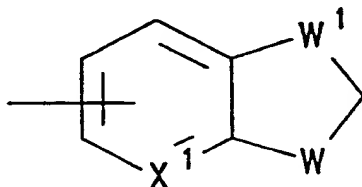
$R^4$  and  $R^5$  each independently represents H,  $C_{1-12}$ alkyl optionally substituted by  $NR^9R^{9'}$  (where  $R^9$  and  $R^{9'}$  are as previously defined) or an azacyclic or azabicyclic group,  $C_{4-9}$ cycloalkyl optionally substituted by one or more  $C_{1-4}$ alkyl groups,  $C_{4-9}$ cycloalkyl $C_{1-4}$ alkyl optionally substituted in the cycloalkyl ring by one or more  $C_{1-4}$ alkyl groups, optionally substituted aryl, optionally substituted aryl $C_{1-6}$ alkyl or azacyclic or azabicyclic groups, or  $R^4$  and  $R^5$  together form the residue of an optionally substituted azacyclic or azabicyclic ring system;

$x$  is 0, 1, 2 or 3;

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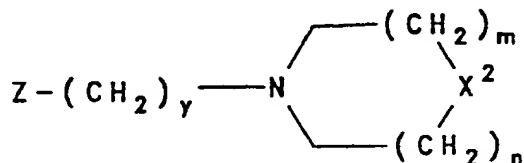
$R^{12}$  represents a phenyl or pyridyl group optionally substituted by one or more substituents selected from  $C_{1-6}$ alkyl, halo, hydroxy,  $C_{1-4}$ alkoxy,  $(CH_2)_q$ -tetrazolyl optionally substituted in the tetrazole ring by  $C_{1-4}$ alkyl,  $(CH_2)_q$ -imidazolyl,  $(CH_2)_q$ -triazolyl (where  $q$  is 0, 1, 2 or 3), 5-hydroxy-4-pyrone,  $NR^6R^7$ ,  $NR^9COR^{11}$ ,  $NR^9CONR^9R^{11}$  (where  $R^9$  and  $R^{9'}$  are each independently H or  $C_{1-4}$ alkyl and  $R^{11}$  is as previously defined),  $CONR^6R^7$  (where  $R^6$  and  $R^7$  are as previously defined),  $SO(C_{1-6}alkyl)$ ,  $SO_2(C_{1-6}alkyl)$ , trifluoromethyl,  $CONHSO_2R^8$ ,  $SO_2NHCOR^8$  (where  $R^8$  is  $C_{1-6}$ alkyl, optionally substituted aryl, 2,2-difluorocyclopropane or trifluoromethyl),  $SO_2NHR^{10}$  (where  $R^{10}$  is a nitrogen containing heterocycle),  $B(OH)_2$ ,  $(CH_2)_qCO_2H$ , where  $q$  is as previously defined; or

$R^{12}$  represents a group



where  $X^1$  represents CH or N; W represents  $CH_2$  or  $NR^9$ , where  $R^9$  is as previously defined, and  $W^1$  represents  $CH_2$ , or W and  $W^1$  each represent O; or

$R^{12}$  represents phenyl substituted by a group

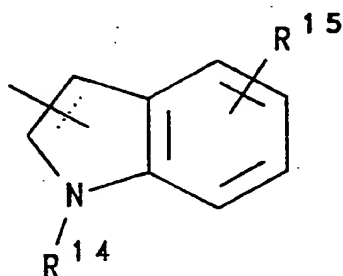


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wherein  $X^2$  is O, S or  $NR^9$ , where  $R^9$  is as previously defined; Z is a bond, O or S; m is 1, 2 or 3; n is 1, 2 or 3; and y is 0, 1, 2 or 3;

$R^{13}$  represents a group

5

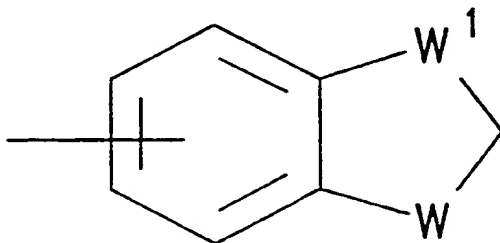


wherein  $R^{14}$  represents H or  $C_{1-6}$ alkyl;  $R^{15}$  represents H,  $C_{1-6}$ alkyl, halo or  $NR^6R^7$ , where  $R^6$  and  $R^7$  are a previously defined; and the dotted line represents an optional covalent bond;

15

and pharmaceutically acceptable salts or prodrugs thereof, with the proviso that, when  $NR^4R^5$  represents an unsubstituted azacyclic ring system,  $R^2$  does not represent  $NHR^{12}$  where  $R^{12}$  is optionally substituted phenyl or

20



It will be appreciated that formula (I) is intended to embrace all possible isomers, including optical isomers, and mixtures thereof, including racemates.

30

As used herein, the definition of each expression, when it occurs more than once in any

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structure, is intended to be independent of its definition elsewhere in the same structure.

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible in vivo into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bungeard, Elsevier, 1985.

Halo includes fluoro, chloro, bromo and iodo. Preferably halo will be fluoro or chloro.

As used herein, unless otherwise indicated, alkyl means straight or branched chain saturated hydrocarbon.

As used herein, azacyclic means non-aromatic nitrogen-containing monocyclic, and azabicyclic means non-aromatic nitrogen-containing bicyclic.

Unless otherwise stated, aryl means optionally substituted carbocyclic or heterocyclic aromatic groups, especially phenyl.

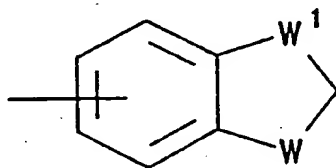
Heteroaryl means aromatic rings preferably having 5 or 6 ring atoms and containing at least one atom selected from O, S and N.

A first subgroup of compounds according to the invention is represented by compounds of formula (I), and salts and prodrugs thereof, wherein  $R^1$  represents  $C_{1-6}$ alkyl,  $C_{3-7}$ cycloalkyl, cyclopropylmethyl,  $CH_2CO_2R^{11}$  or  $CH_2CONR^6R^7$ ;  $R^2$  represents  $NHR^{12}$  where  $R^{12}$  represents a phenyl group optionally substituted by one or more substituents selected from  $C_{1-6}$ alkyl, halo, hydroxy,  $C_{1-4}$ alkoxy,  $(CH_2)_q$ -tetrazolyl optionally substituted in the tetrazole ring by  $C_{1-4}$ alkyl,  $(CH_2)_q$ -imidazolyl,

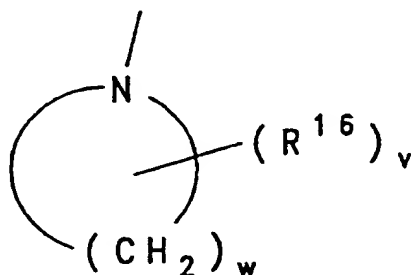
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(CH<sub>2</sub>)<sub>q</sub>-triazolyl, 5-hydroxy-4-pyrone, NR<sup>6</sup>R<sup>7</sup>, NR<sup>9</sup>COR<sup>11</sup>,  
 NR<sup>9</sup>CONR<sup>9'</sup>R<sup>11</sup>, CONR<sup>6</sup>R<sup>7</sup>, SO(C<sub>1-6</sub>alkyl), SO<sub>2</sub>(C<sub>1-6</sub>alkyl),  
 trifluoromethyl, CONHSO<sub>2</sub>R<sup>8</sup>, SO<sub>2</sub>NHCOR<sup>8</sup>, SO<sub>2</sub>NHR<sup>10</sup>, B(OH)<sub>2</sub>  
 and (CH<sub>2</sub>)<sub>t</sub>CO<sub>2</sub>H, where t is zero, 1 or 2; or

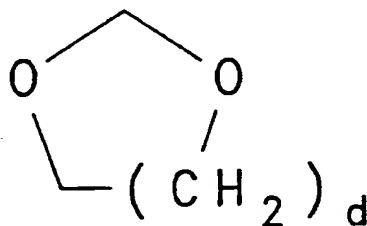
5 R<sup>12</sup> represents a group



and NR<sup>4</sup>R<sup>5</sup> represents a group



20 wherein each R<sup>16</sup> independently represents C<sub>1-6</sub>alkyl,  
 C<sub>1-6</sub>alkoxy, hydroxy, oxo, SR<sup>11</sup>, NR<sup>6</sup>R<sup>7</sup>, NR<sup>9</sup>C<sub>1-4</sub>alkylR<sup>17</sup>,  
 =NOR<sup>9</sup> or

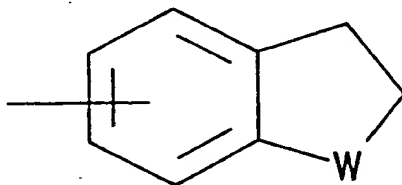


30 where R<sup>11</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>9</sup> are as previously defined, R<sup>17</sup>  
 is halo or trifluoromethyl, and d is 2 or 3; v is 1, 2,  
 3, 4, 5, 6, 7 or 8; and w is 4, 5, 6, 7, 8, 9, 10 or 11.

Within the abovementioned subgroup of compounds  
 according to the invention there may be identified a  
 subclass of compounds of formula (I), and salts and  
 prodrugs thereof, wherein R<sup>12</sup> represents a phenyl group

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optionally substituted by one or more substituents selected from C<sub>1-6</sub>alkyl, halo, hydroxy, C<sub>1-4</sub>alkoxy, (CH<sub>2</sub>)<sub>q</sub>-tetrazolyl optionally substituted in the tetrazole ring by C<sub>1-4</sub>alkyl, (CH<sub>2</sub>)<sub>q</sub>-imidazolyl, (CH<sub>2</sub>)<sub>q</sub>-triazolyl, 5-hydroxy-4-pyrone, NR<sup>6</sup>R<sup>7</sup>, NR<sup>9</sup>COR<sup>11</sup>, NR<sup>9</sup>COR<sup>9'</sup>R<sup>11</sup>, CONR<sup>6</sup>R<sup>7</sup>, SO(C<sub>1-6</sub>alkyl), SO<sub>2</sub>(C<sub>1-6</sub>alkyl), trifluoromethyl, CONHSO<sub>2</sub>R<sup>8</sup>, SO<sub>2</sub>NHCOR<sup>8</sup>, SO<sub>2</sub>NHR<sup>10</sup>, B(OH)<sub>2</sub> and (CH<sub>2</sub>)<sub>t</sub>CO<sub>2</sub>H; or R<sup>12</sup> represents a group



where W represents CH<sub>2</sub> or NR<sup>9</sup>;

R<sup>16</sup> represents C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, hydroxy, oxo, SR<sup>11</sup>, NR<sup>6</sup>R<sup>7</sup>, NR<sup>9</sup>C<sub>1-4</sub>alkylR<sup>17</sup>, =NOR<sup>9</sup> or OR<sup>18</sup> OR<sup>19</sup>,

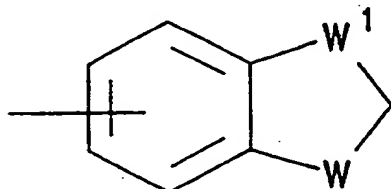
where R<sup>18</sup> and R<sup>19</sup> each independently represent C<sub>1-4</sub>alkyl or R<sup>18</sup> and R<sup>19</sup> together form a chain CH<sub>2</sub>CH<sub>2</sub> or CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>; and v is 1.

A second subgroup of compounds according to the invention is represented by compounds of formula (I), and salts and prodrugs thereof, wherein R<sup>1</sup> represents H, C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl, cyclopropylmethyl, (CH<sub>2</sub>)<sub>r</sub>imidazolyl, (CH<sub>2</sub>)<sub>r</sub>triazolyl, (CH<sub>2</sub>)<sub>r</sub>tetrazolyl, CH<sub>2</sub>CO<sub>2</sub>R<sup>11</sup> or CH<sub>2</sub>CONR<sup>6</sup>R<sup>7</sup>; R<sup>2</sup> is NHR<sup>12</sup> where R<sup>12</sup> represents a phenyl group optionally substituted by one or more substituents selected from C<sub>1-6</sub>alkyl, halo, hydroxy, C<sub>1-4</sub>alkoxy, (CH<sub>2</sub>)<sub>q</sub>-tetrazolyl optionally substituted in the tetrazole ring by C<sub>1-4</sub>alkyl, (CH<sub>2</sub>)<sub>q</sub>-imidazolyl, (CH<sub>2</sub>)<sub>q</sub>-triazolyl, 5-hydroxy-4-pyrone, NR<sup>6</sup>R<sup>7</sup>, NR<sup>9</sup>COR<sup>11</sup>, NR<sup>9</sup>CONR<sup>9'</sup>R<sup>11</sup>, CONR<sup>6</sup>R<sup>7</sup>, SO(C<sub>1-6</sub>alkyl), SO<sub>2</sub>(C<sub>1-6</sub>alkyl), trifluoromethyl, CONHSO<sub>2</sub>R<sup>8</sup>, SO<sub>2</sub>NHCOR<sup>8</sup>, SO<sub>2</sub>NHR<sup>10</sup>, B(OH)<sub>2</sub> and (CH<sub>2</sub>)<sub>q</sub>CO<sub>2</sub>H; or



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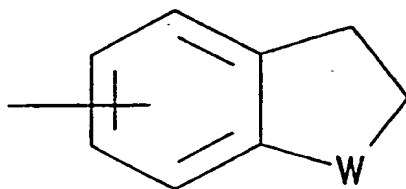
$R^{12}$  represents a group



and  $R^4$  and  $R^5$  together form the residue of a bridged azabicyclic ring system.

Within the abovementioned second subgroup of compounds according to the invention there may be identified a subclass of compounds of formula (I), and salts and prodrugs thereof, wherein  $R^1$  represents  $C_{1-6}$ alkyl,  $C_{3-7}$ cycloalkyl, cyclopropylmethyl,  $CH_2CO_2R^{11}$  or  $CH_2CONR^6R^7$ ; and  $R^{12}$  represents a phenyl group optionally substituted by one or more substituents selected from  $C_{1-6}$ alkyl, halo, hydroxy,  $C_{1-4}$ alkoxy,  $(CH_2)_q$ -tetrazolyl optionally substituted in the tetrazole ring by  $C_{1-4}$ alkyl,  $(CH_2)_q$ -imidazolyl,  $(CH_2)_q$ triazolyl, 5-hydroxy-4-pyrone,  $NR^6R^7$ ,  $NR^9COR^{11}$ ,  $NR^9COR^{9'}R^{11}$ ,  $CONR^6R^7$ ,  $SO(C_{1-6}alkyl)$ ,  $SO_2(C_{1-6}alkyl)$ , trifluoromethyl,  $CONHSO_2R^8$ ,  $SO_2NHCOR^8$ ,  $SO_2NHR^{10}$ ,  $B(OH)_2$  and  $(CH_2)_tCO_2H$ , where  $t$  is zero, 1 or 2; or

$R^{12}$  represents a group

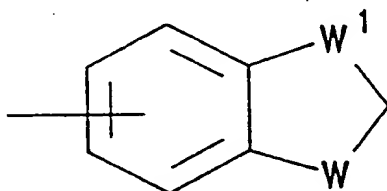


where  $W$  represents  $CH_2$  or  $NR^9$ .

A third subgroup of compounds according to the invention is represented by compounds of formula (I), and salts and prodrugs thereof, wherein  $R^1$  represents  $H$ ,  $C_{1-6}$ alkyl,  $C_{3-7}$ cycloalkyl, cyclopropylmethyl,  $CH_2CO_2R^{11}$  or  $CH_2CONR^6R^7$ ;  $R^{12}$  represents a phenyl group optionally

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substituted by one or more substituents selected from C<sub>1-6</sub>alkyl, halo, hydroxy, C<sub>1-4</sub>alkoxy, (CH<sub>2</sub>)<sub>q</sub>-tetrazolyl optionally substituted in the tetrazole ring by C<sub>1-4</sub>alkyl, (CH<sub>2</sub>)<sub>q</sub>-imidazolyl, (CH<sub>2</sub>)<sub>q</sub>-triazolyl, 5-hydroxy-4-pyrone, NR<sup>6</sup>R<sup>7</sup>, NR<sup>9</sup>COR<sup>11</sup>, NR<sup>9</sup>CONR<sup>9'</sup>R<sup>11</sup>, CONR<sup>6</sup>R<sup>7</sup>, SO(C<sub>1-6</sub>alkyl), SO<sub>2</sub>(C<sub>1-6</sub>alkyl), trifluoromethyl, CONHSO<sub>2</sub>R<sup>8</sup>, SO<sub>2</sub>NHCOR<sup>8</sup>, SO<sub>2</sub>NHR<sup>10</sup>, B(OH)<sub>2</sub> and (CH<sub>2</sub>)<sub>q</sub>CO<sub>2</sub>H; or R<sup>12</sup> represents a group

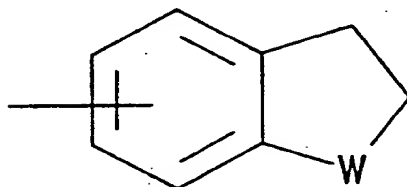


and R<sup>4</sup> and R<sup>5</sup> are independently selected from H, C<sub>1-12</sub>alkyl, C<sub>4-9</sub>cycloalkyl(CH<sub>2</sub>)<sub>k</sub> optionally substituted by one or more C<sub>1-4</sub>alkyl groups, bridged C<sub>6-10</sub>bicycloalkyl, (CH<sub>2</sub>)<sub>k</sub>R<sup>20</sup> (where R<sup>20</sup> is NR<sup>6</sup>R<sup>7</sup> as previously defined, or an azacyclic or azabicyclic group and k is 0, 1, 2, 3 or 4), optionally substituted aryl, and optionally substituted arylC<sub>1-6</sub>alkyl.

Within this third subgroup of compounds according to the invention there may be identified a subclass of compounds of formula (I), and salts and prodrugs thereof, wherein R<sup>1</sup> represents C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl, cyclopropylmethyl, CH<sub>2</sub>CO<sub>2</sub>R<sup>11</sup> or CH<sub>2</sub>CONR<sup>6</sup>R<sup>7</sup>; and R<sup>12</sup> represents a phenyl group optionally substituted by one or more substituents selected from C<sub>1-6</sub>alkyl, halo, hydroxy, C<sub>1-4</sub>alkoxy, (CH<sub>2</sub>)<sub>q</sub>-tetrazolyl optionally substituted in the tetrazole ring by C<sub>1-4</sub>alkyl, (CH<sub>2</sub>)<sub>q</sub>-imidazolyl, (CH<sub>2</sub>)<sub>q</sub>-triazolyl, 5-hydroxy-4-pyrone, NR<sup>6</sup>R<sup>7</sup>, NR<sup>9</sup>COR<sup>11</sup>, NR<sup>9</sup>COR<sup>9'</sup>R<sup>11</sup>, CONR<sup>6</sup>R<sup>7</sup>, SO(C<sub>1-6</sub>alkyl), SO<sub>2</sub>(C<sub>1-6</sub>alkyl), trifluoromethyl, CONHSO<sub>2</sub>R<sup>8</sup>, SO<sub>2</sub>NHCOR<sup>8</sup>, SO<sub>2</sub>NHR<sup>10</sup>, B(OH)<sub>2</sub> and (CH<sub>2</sub>)<sub>t</sub>CO<sub>2</sub>H, where t is zero, 1 or 2; or

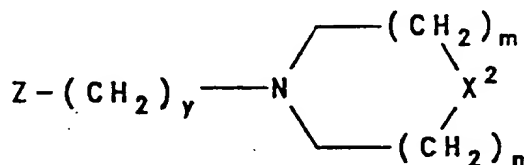
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$R^{12}$  represents a group



where W represents  $CH_2$  or  $NR^9$ ; and  $R^4$  and  $R^5$  are independently selected from H,  $C_{1-12}$ alkyl,  $C_{4-9}$ cycloalkyl, optionally substituted aryl, optionally substituted aryl $C_{1-6}$ alkyl, and azacyclic and azabicyclic groups.

A fourth subgroup of compounds according to the invention is represented by compounds of formula (I), and salts and prodrugs thereof, wherein  $R^1$  represents  $C_{1-6}$ alkyl,  $C_{3-7}$ cycloalkyl, cyclopropylmethyl,  $CH_2CO_2R^{11}$  or  $CH_2CONR^6R^7$ ;  $R^2$  represents  $NHR^{12}$  where  $R^{12}$  represents phenyl substituted by a group

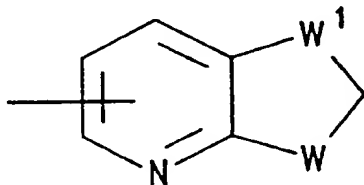


and  $R^4$  and  $R^5$  each independently represents H,  $C_{1-12}$ alkyl,  $C_{4-9}$ cycloalkyl, optionally substituted aryl, optionally substituted aryl $C_{1-6}$ alkyl or an azacyclic or azabicyclic group, or  $R^4$  and  $R^5$  together form the residue of an azacyclic or a bridged azabicyclic ring system.

A fifth subgroup of compounds according to the invention is represented by compounds of formula (I), and salts and prodrugs thereof, wherein  $R^1$  represents H,  $C_{1-6}$ alkyl,  $C_{3-7}$ cycloalkyl, cyclopropylmethyl,

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(CH<sub>2</sub>)<sub>r</sub>imidazolyl, (CH<sub>2</sub>)<sub>r</sub>triazolyl, (CH<sub>2</sub>)<sub>r</sub>tetrazolyl, CH<sub>2</sub>CO<sub>2</sub>R<sup>11</sup> or CH<sub>2</sub>CONR<sup>6</sup>R<sup>7</sup>; R<sup>2</sup> represents NHR<sup>12</sup> where R<sup>12</sup> represents a pyridyl group optionally substituted by one or more substituents selected from C<sub>1-6</sub>alkyl, halo, hydroxy, C<sub>1-4</sub>alkoxy, (CH<sub>2</sub>)<sub>q</sub>-tetrazolyl optionally substituted in the tetrazole ring by C<sub>1-4</sub>alkyl, (CH<sub>2</sub>)<sub>q</sub>-imidazolyl, (CH<sub>2</sub>)<sub>q</sub>-triazolyl, 5-hydroxy-4-pyrone, NR<sup>6</sup>R<sup>7</sup>, NR<sup>9</sup>COR<sup>11</sup>, NR<sup>9</sup>CONR<sup>9'</sup>R<sup>11</sup>, CONR<sup>6</sup>R<sup>7</sup>, SO(C<sub>1-6</sub>alkyl), SO<sub>2</sub>(C<sub>1-6</sub>alkyl), trifluoromethyl, CONHSO<sub>2</sub>R<sup>8</sup>, SO<sub>2</sub>NHCOR<sup>8</sup>, SO<sub>2</sub>NHR<sup>10</sup>, B(OH)<sub>2</sub> and (CH<sub>2</sub>)<sub>q</sub>CO<sub>2</sub>H; or R<sup>12</sup> represents a group



and R<sup>4</sup> and R<sup>5</sup> each independently represents H, C<sub>1-12</sub>alkyl, C<sub>4-9</sub>cycloalkyl optionally substituted by one or more C<sub>1-4</sub>alkyl groups, C<sub>4-9</sub>cycloalkylC<sub>1-4</sub>alkyl, optionally substituted aryl, optionally substituted arylC<sub>1-6</sub>alkyl or an azacyclic or azabicyclic group, or R<sup>4</sup> and R<sup>5</sup> together form the residue of an optionally substituted azacyclic or a bridged azabicyclic ring system.

A sixth subgroup of compounds according to the invention is represented by compounds of formula (I), and salts and prodrugs thereof, wherein R<sup>1</sup> represents H, C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl, cyclopropylmethyl, (CH<sub>2</sub>)<sub>r</sub>imidazolyl, (CH<sub>2</sub>)<sub>r</sub>triazolyl, (CH<sub>2</sub>)<sub>r</sub>tetrazolyl, CH<sub>2</sub>CO<sub>2</sub>R<sup>11</sup> or CH<sub>2</sub>CONR<sup>6</sup>R<sup>7</sup>; R<sup>2</sup> represents (CH<sub>2</sub>)<sub>s</sub>R<sup>13</sup>; and R<sup>4</sup> and R<sup>5</sup> together form the residue of an azacyclic or azabicyclic ring system.

A seventh subgroup of compounds according to the invention is represented by compounds of formula (I),

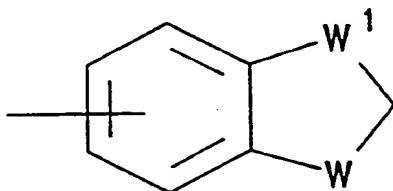
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and salts and prodrugs thereof, wherein  $R^1$  represents H,  $C_{1-6}$ alkyl,  $C_{3-7}$ cycloalkyl, cyclopropylmethyl,  $(CH_2)_r$ imidazolyl,  $(CH_2)_r$ triazolyl,  $(CH_2)_r$ tetrazolyl,  $CH_2CO_2R^{11}$  or  $CH_2CONR^6R^7$ ;  $R^2$  is  $NHR^{12}$  where  $R^{12}$  represents

5 a phenyl group optionally substituted by one or more substituents selected from  $C_{1-6}$ alkyl, halo, hydroxy,  $C_{1-4}$ alkoxy,  $(CH_2)_q$ -tetrazolyl optionally substituted in the tetrazole ring by  $C_{1-4}$ alkyl,  $(CH_2)_q$ -imidazolyl,  $(CH_2)_q$ -triazolyl, 5-hydroxy-4-pyrone,  $NR^6R^7$ ,  $NR^9COR^{11}$ ,

10  $NR^9CONR^9R^{11}$ ,  $CONR^6R^7$ ,  $SO(C_{1-6}alkyl)$ ,  $SO_2(C_{1-6}alkyl)$ , trifluoromethyl,  $CONHSO_2R^8$ ,  $SO_2NHCOR^8$ ,  $SO_2NHR^{10}$ ,  $B(OH)_2$  and  $(CH_2)_qCO_2H$ ; or

$R^{12}$  represents a group



and  $R^4$  and  $R^5$  together form the residue of a fused or

20 spiro azabicyclic ring system.

When  $R^1$  is  $C_{3-7}$ cycloalkyl, suitable cycloalkyl groups include cyclopropyl, cyclopentyl and cyclohexyl groups, preferably cyclopropyl.

Preferably  $R^1$  represents  $C_{1-6}$ alkyl optionally

25 substituted by one or more halo, such as  $C_{1-4}$ alkyl optionally substituted by one, two or three fluoro. Preferred values for  $R^1$  include methyl, ethyl, n-propyl, i-butyl and 2,2,2-trifluoroethyl.

When  $R^2$  represents  $NHR^{12}$  and  $R^{12}$  represents

30 phenyl or pyridyl substituted by  $CONHSO_2R^8$  or  $SO_2NHCOR^8$ , suitable values for  $R^8$  include  $C_{1-6}$ alkyl, optionally substituted aryl and trifluoromethyl.

When  $R^8$  is optionally substituted aryl, this will preferably be optionally substituted phenyl.

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Suitable substituents include C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, halo and trifluoromethyl. Preferred is unsubstituted phenyl or phenyl substituted by C<sub>1-6</sub>alkyl, such as methyl, for example, phenyl substituted by C<sub>1-6</sub>alkyl in the ortho position.

When R<sup>8</sup> is C<sub>1-6</sub>alkyl, it will preferably represent C<sub>1-4</sub>alkyl. Particularly preferred are methyl and iso-propyl, especially iso-propyl.

When R<sup>12</sup> is phenyl or pyridyl substituted by SO<sub>2</sub>NHR<sup>10</sup>, suitable values of R<sup>10</sup> include, for example, thiazole, thiadiazole and pyrazine.

Preferably q is zero.

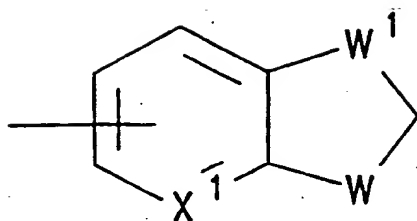
When R<sup>2</sup> represents NHR<sup>12</sup>, and R<sup>12</sup> represents optionally substituted phenyl or pyridyl, the substituents will preferably be selected from C<sub>1-6</sub>alkyl, such as methyl and ethyl, halo, such as chloro, bromo, fluoro and iodo, and trifluoromethyl.

When R<sup>12</sup> represents monosubstituted phenyl, the substituent will preferably be located at the 3- or 4-position of the phenyl ring, more preferably at the 3-position. When R<sup>12</sup> represents disubstituted phenyl the substituents will preferably be located at the 3- and 4-positions of the phenyl ring.

When R<sup>12</sup> represents optionally substituted pyridyl it will preferably represent optionally substituted 3-pyridyl. When R<sup>12</sup> represents monosubstituted 3-pyridyl, the substituent will preferably be located at the 5-position of the pyridyl ring.

When R<sup>12</sup> represents a group

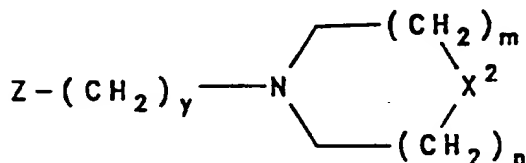
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where  $X^1$  is CH the fused 5-membered ring will preferably be fused across the 3- and 4-positions of the phenyl ring and where  $X^1$  is N the 5-membered ring will preferably be fused across the 4- and 5-positions of the phenyl ring.

Preferably W and  $W^1$  are  $CH_2$ .

When  $R^{12}$  represents phenyl substituted by a group



the substituent will preferably be located at the 3- or 4- position of the phenyl ring, more preferably at the 3- position.

25 Preferably m is 1 or 2, more preferably 1.  
 Preferably n is 1 or 2, more preferably 1.  
 Preferably y is 0 or 1, more preferably 0.  
 Suitable values for  $X^2$  include O, S, NH and

$NCH_3$ .

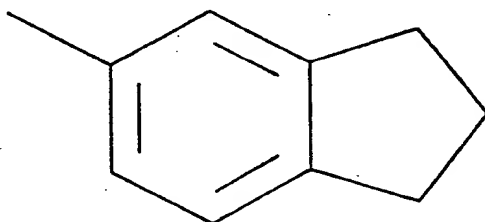
30 Preferably Z represents a bond.

When  $R^2$  represents  $(CH_2)_s R^{13}$ , s is preferably 0 or 1, more preferably 0,  $R^{14}$  is preferably H and  $R^{15}$  is preferably H. The optional covalent bond may suitably be either present or absent, preferably present.

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Particularly preferred are compounds of formula (I) wherein  $R^2$  represents  $NHR^{12}$  and  $R^{12}$  represents phenyl substituted by one or two substituents selected from  $C_{1-6}$ alkyl, halo and trifloromethyl; or  $R^{12}$  represents

5



Suitable values for  $R^3$  include methyl and dimethylamino.

Preferably  $x$  is 0 or 1, more preferably 0.

When  $R^4$  or  $R^5$  represents optionally substituted  
15 aryl or optionally substituted aryl $C_{1-6}$ alkyl, suitable aryl groups include phenyl, thienyl, furyl, pyrrolyl and pyridyl, preferably phenyl. Suitable aryl substituents include, for example,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, halo and trifluoromethyl.

20 When  $R^4$  or  $R^5$  represents an azacyclic or azabicyclic group, or  $C_{1-6}$ alkyl substituted by an azacyclic or azabicyclic group, the azacyclic or azabicyclic group may contain, in addition to the nitrogen atom, a further heteroatom selected from O and  
25 S, or a group  $NR^{21}$ , where  $R^{21}$  is H or  $C_{1-4}$ alkyl.

When  $R^4$  or  $R^5$  represents an azacyclic group or  $C_{1-6}$ alkyl substituted by an azacyclic group, the azacyclic group will suitably contain from 5 to 10 ring atoms.

30 When  $R^4$  or  $R^5$  represents an azabicyclic group or  $C_{1-6}$ alkyl substituted by an azabicyclic group, the azabicyclic group will suitably contain from 7 to 10 ring atoms.



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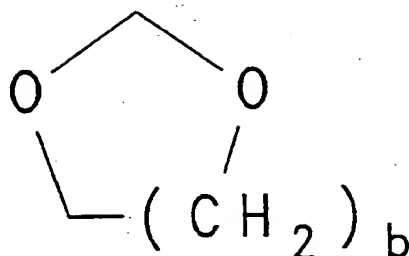
When  $R^4$  or  $R^5$  represents  $C_{4-9}$ cycloalkyl substituted by one or more  $C_{1-4}$ alkyl groups or  $C_{4-9}$ cycloalkyl $C_{1-4}$ alkyl substituted in the cycloalkyl ring by one or more  $C_{1-4}$ alkyl groups, the  $C_{1-4}$ alkyl groups may be located on any available ring carbon atom. In particular, geminal disubstitution is provided for. The  $C_{1-4}$ alkyl groups will preferably be methyl groups.

Suitably  $R^4$  and  $R^5$  are selected from H,  $C_{1-6}$ alkyl, such as methyl, ethyl and n-propyl,  $C_{4-9}$ cycloalkyl, such as cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl, optionally substituted by one or more methyl groups,  $C_{4-9}$ cycloalkyl $C_{1-4}$ alkyl, such as cyclohexylmethyl, aryl $C_{1-6}$ alkyl, such as benzyl,  $C_{1-6}$ alkyl substituted by  $NR^9R^{9'}$ , such as  $CH_2CH_2N(CH_3)_2$ ,  $C_{1-6}$ alkyl substituted by an azacyclic group, such as  $C_{1-4}$ alkyl substituted by morpholinyl, and azacyclic groups, such as N-methylpiperidine.

When  $R^4$  and  $R^5$  together form the residue of an azacyclic or azabicyclic ring system, the azacyclic or azabicyclic ring system may contain, in addition to the nitrogen atom to which  $R^4$  and  $R^5$  are attached, a second heteroatom selected from O, S or a group  $NR^{22}$ , where  $R^{22}$  is H,  $C_{1-4}$ alkyl,  $CO_2R^a$ ,  $COR^a$  or  $SO_2R^a$  where  $R^a$  is  $C_{1-6}$ alkyl, optionally substituted phenyl or benzyl optionally substituted in the phenyl ring by one or more substituents, where the phenyl substituents are selected from  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, halo and trifluoromethyl.

When  $R^4$  and  $R^5$  together form the residue of an azacyclic ring system, the ring system may be substituted by one or more groups selected from  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy, hydroxy, halo, trifluoromethyl, oxo,  $SR^{11}$ ,  $NR^6R^7$ ,  $NR^9C_{1-4}alkylR^{23}$ ,  $=NOR^9$  or

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where  $R^6$ ,  $R^7$ ,  $R^9$  and  $R^{11}$  are as previously defined,  $R^{23}$  is halo or trifluoromethyl, and  $b$  is 2 or 3. The substituents may be located on any available carbon atom. In particular, geminal disubstitution is provided for where appropriate. Particularly suitable substituents include oxo, ketyl,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy, trifluoromethyl and  $NHC_{1-4}alkylCF_3$  groups. Preferred are  $C_{1-6}$ alkyl groups, especially methyl.

When  $R^4$  and  $R^5$  form the residue of an azacyclic ring system, the ring system suitably contains from 5 to 10 ring atoms, preferably 6, 7 or 8 ring atoms, more preferably 7 ring atoms.

When  $R^4$  and  $R^5$  together form the residue of an azabicyclic ring system, the azabicyclic ring system may be fused, spiro or bridged, preferably fused or bridged, more preferably bridged. The azabicyclic ring system may optionally be substituted by one or more  $C_{1-4}$ alkyl, such as methyl, groups. The alkyl substituents may be located on any available carbon atoms of the azabicyclic ring system. In particular, geminal disubstitution is provided for.

Preferably the azabicyclic ring system is unsubstituted.

Suitably the azabicyclic ring system contains from 7 to 10 ring atoms, preferably 7, 8 or 9 ring atoms.

Particularly preferred are compounds of formula (I) wherein  $R^4$  and  $R^5$  together form the residue of an

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azacyclic ring system substituted by one or more methyl groups, or R<sup>4</sup> and R<sup>5</sup> together form the residue of a bridged azabicyclic ring system, especially 3-azabicyclo[3.2.2]nonan-3-yl.

5                    Preferably the salts of the compounds of formula (I) are pharmaceutically acceptable, but non-pharmaceutically acceptable salts may be used for the preparation of pharmaceutically acceptable salts. The pharmaceutically acceptable salts of the compounds of  
10 formula (I) include the conventional non-toxic salts or the quaternary ammonium salts of the compounds from formula (I) formed, e.g., from non-toxic inorganic or organic acids or bases. For example, such conventional non-toxic salts include those derived from inorganic  
15 acids such as hydrochloric, hydrobromic, sulphuric, sulphamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, steric, lactic, malic, tartaric, citric, ascorbic, palmoic, maleic, hydroxymaleic,  
20 phenylacetic, glutamic, benzoic, salicylic, sulphanilic, 2-acetoxy benzoic, fumaric, toluenesulphonic, methanesulphonic, ethane disulphonic, oxalic and isothionic.

25                    The salts of the present invention can be synthesized from the compound of formula (I) which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired  
30 salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

                  The present invention also encompasses a pharmaceutical composition comprising a compound of

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formula (I), or a salt or prodrug thereof and a pharmaceutically acceptable carrier.

5 The compounds of formula (I) and their salts and prodrugs, may be administered to animals, preferably to mammals, and most especially to a human subject either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard  
10 pharmaceutical practice. The compounds can be administered orally, parenterally, including by intravenous, intramuscular, intraperitoneal or subcutaneous administration, or topically.

For oral use of an antagonist of CCK, according  
15 to this invention, the selected compounds may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and  
20 lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and  
25 suspending agents. If desired, certain sweetening and/or flavouring agents may be added.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of  
30 the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

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For topical administration, a compound of formula (I) may be formulated as, for example, a suspension, lotion, cream or ointment.

For topical administration, pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or arylalkanols, vegetable oils, polyalkylene glycols, petroleum based jelly, ethyl cellulose, ethyl oleate, carboxymethylcellulose, polyvinylpyrrolidone, isopropyl myristate and other conventionally-employed non-toxic, pharmaceutically acceptable organic and inorganic carriers. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting agents, bodying agents and the like, as for example, polyethylene glycols 200, 300, 400 and 600, carbowaxes 1,000, 1,500, 4,000, 5,000 and 10,000, antibacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and which are non-injurious in use, thimerosal, methyl and propyl paraben, benzyl alcohol, phenyl ethanol, buffering ingredients such as sodium chloride, sodium borate, sodium acetates, gluconate buffers, and other conventional ingredients such as sorbitan monolaurate, triethanolamine, oleate, polyoxyethylene sorbitan monopalmitate, dioctyl sodium sulfosuccinate, monothioglycerol, thiosorbitol, ethylenediamine tetraacetic acid, and the like.

The compounds of formula (I) antagonise CCK and/or gastrin and are useful for the treatment and prevention of disorders including central nervous system disorders wherein CCK and/or gastrin may be involved. Examples of such disease states include gastrointestinal diseases, including gastrointestinal ulcers, such as peptic and duodenal ulcers, irritable bowel syndrome,

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gastroesophagenal reflux disease or excess pancreatic or gastrin secretion, acute pancreatitis, or motility disorders; central nervous system disorders, including central nervous system disorders caused by CCK

5 interaction with dopamine, serotonin and other monoamine neurotransmitters, such as neuroleptic disorders, tardive dyskinesia, Parkinson's disease, psychosis or Gilles de la Tourette syndrome; depression such as depression resulting from organic disease, secondary to stress  
10 associated with personal loss, or idiopathic depression; schizophrenia; disorders of appetite regulatory systems; Zollinger-Ellison syndrome, antral and cell hyperplasia, or pain.

The compounds of formula (I) are particularly  
15 useful in the treatment or prevention of neurological disorders involving anxiety disorders and panic disorders, wherein CCK and/or gastrin is involved. Examples of such disorders include panic disorders, anxiety disorders, panic syndrome, anticipatory anxiety,  
20 phobic anxiety, panic anxiety, chronic anxiety and endogenous anxiety.

The compounds of formula (I) are also useful for directly inducing analgesia, opiate or non-opiate mediated, as well as anesthesia or loss of the sensation  
25 of pain.

The compounds of formula (I) may further be useful for preventing or treating the withdrawal response produced by chronic treatment or abuse of drugs or alcohol. Such drugs include, but are not limited to  
30 benzodiazepines, cocaine, alcohol and nicotine.

The compounds of formula (I) may further be useful in the treatment of stress and its relationship with drug abuse.

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The compounds of formula (I) may further be useful in the treatment of oncologic disorders wherein CCK may be involved. Examples of such oncologic disorders include small cell adenocarcinomas and primary  
5 tumours of the central nervous system glial and neuronal cells. Examples of such adenocarcinomas and tumours include, but are not limited to, tumours of the lower oesophagus, stomach, intestine, colon and lung, including small cell lung carcinoma.

10 The compounds of formula (I) may also be useful as neuroprotective agents, for example, in the treatment and/or prevention of neurodegenerative disorders arising as a consequence of such pathological conditions as stroke, hypoglycaemia, cerebral palsy, transient cerebral  
15 ischaemic attack, cerebral ischaemia during cardiac pulmonary surgery or cardiac arrest, perinatal asphyxia, epilepsy, Huntington's chorea, Alzheimer's disease, Amyotrophic Lateral Sclerosis, Parkinson's disease, Olivo-ponto-cerebellar atrophy, anoxia such as from  
20 drowning, spinal cord and head injury, and poisoning by neurotoxins, including environmental neurotoxins.

The compounds of formula (I) may further be used to induce miosis for therapeutic purposes after certain types of examination and intraocular surgery. An  
25 example of intraocular surgery would include cataract surgery with implantation of an artificial lens. The CCK antagonist compounds of this invention can be used to prevent miosis occurring in association with iritis, ureitis and trauma.

30 The present invention therefore provides a compound of formula (I) or a salt or prodrug thereof for use in the preparation of a medicament.

The present invention also provides a compound of formula (I) for use in therapy.

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In a further or alternative embodiment the present invention provides a method for the treatment or prevention of a physiological disorder involving CCK and/or gastrin which method comprises administration to a patient in need thereof of a CCK and/or gastrin antagonising amount of a compound of formula (I).

When a compound according to formula (I) is used as an antagonist of CCK or gastrin in a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms. However, in most instances, an effective daily dosage will be in the range from about 0.005mg/kg to about 100mg/kg of body weight, and preferably, of from 0.05mg/kg to about 50mg/kg, such as from about 0.5mg/kg to about 20mg/kg of body weight, administered in single or divided doses. In some cases, however, it may be necessary to use dosages outside these limits. For example, animal experiments have indicated that doses as low as 1ng may be effective.

In effective treatment of panic syndrome, panic disorder, anxiety disorder and the like, preferably about 0.05 mg/kg to about 0.5 mg/kg of CCK antagonist may be administered orally (p.o.), administered in single or divided doses per day (b.i.d.). Other routes of administration are also suitable.

For directly inducing analgesia, anaesthesia or loss of pain sensation, the effective dosage preferably ranges from about 100 ng/kg to about 1mg/kg by systemic administration. Oral administration is an alternative route, as well as others.

In the treatment of irritable bowel syndrome, preferably about 0.1 to 10 mg/kg of CCK antagonist is



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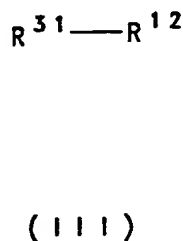
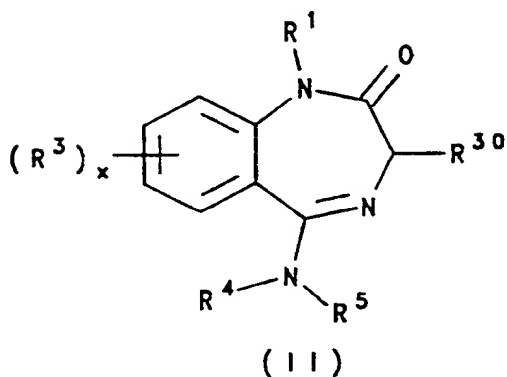
administered orally (p.o.), administered in single or divided doses per day (b.i.d.). Other routes of administration are also suitable.

5 The use of a gastrin antagonist as a tumour palliative for gastrointestinal neoplasma with gastrin receptors, as a modulator of central nervous activity, treatment of Zollinger-Ellison syndrome, or in the treatment of peptic ulcer disease, an effective dosage of preferably about 0.1 to about 10 mg/kg administered one-  
10 to-four times daily is indicated.

For use as neuroprotective agents the effective dosage preferably ranges from about 0.5mg/kg to about 20mg/kg.

15 Because these compounds antagonise the function of CCK in animals, they may also be used as feed additives to increase the food intake of animals in daily dosage of preferably about 0.05mg/kg to about 50mg/kg of body weight.

20 The compounds of formula (I) wherein  $R^2$  is  $NHR^{12}$  may be prepared by reaction of intermediates of formula (II) with compounds of formula (III)



wherein  $R^1$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^{12}$  and  $x$  are as defined for formula (I) above, one of  $R^{30}$  and  $R^{31}$  represents  $NH_2$  and the other of  $R^{30}$  and  $R^{31}$  represents  $-N=C=O$ .

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The reaction is conveniently effected in a suitable organic solvent, such as an ether, for example, tetrahydrofuran.

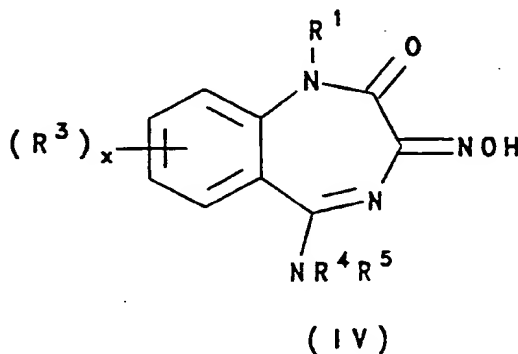
The compounds of formula (I) wherein  $R^2$  is  $(CH_2)_sR^{13}$  may be prepared by reaction of intermediates of formula (II) wherein  $R^{30}$  is  $NH_2$  (hereinafter intermediates (IIA)) with compounds of formula  $HOC(=O)(CH_2)_sR^{13}$ , wherein  $s$  and  $R^{13}$  are as previously defined, in the presence of a base and a coupling reagent.

Suitable bases of use in the reaction include tertiary amines such as, for example, triethylamine.

A preferred coupling agent for use in the reaction is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), preferably in the presence of 1-hydroxybenzotriazole.

The reaction is conveniently effected in a suitable organic solvent, such as, for example, dimethylformamide.

Intermediates of formula (IIA) may be prepared from compounds of formula (IV):



wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$  and  $x$  are as defined for formula (I) above, by reduction, for example, by

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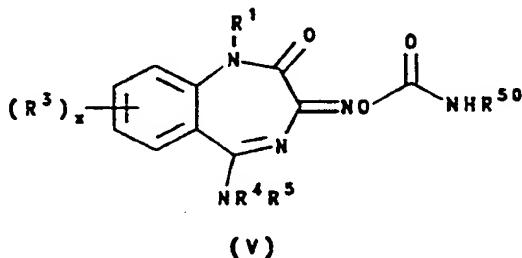
catalytic hydrogenation or reduction using a suitable metal under acidic conditions.

Suitable hydrogenation catalysts include, for example, nobel metal catalysts, e.g. ruthenium, or rhodium which may be supported, for example, on carbon.

The reaction is preferably conducted in a suitable organic solvent, such as an alcohol, for example, methanol, at elevated temperature, e.g. about 60°C.

Suitable reduction methods using metals include, for example, the use of zinc and trifluoroacetic acid in a suitable solvent, such as acetic acid, preferably at elevated temperature, e.g. at about 40°C.

Preferably, intermediates of formula (IIA) may be prepared from compounds of formula (V)



wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$  and  $x$  are as defined for formula (I) and  $R^{50}$  represents  $C_{1-4}$ alkyl, by reduction, for example, by catalytic hydrogenation.

Suitable hydrogenation catalysts include, for example, nobel metal catalysts, such as palladium, which may be supported, for example, on carbon.

The reaction is conveniently conducted in a suitable organic solvent, such as an alcohol, for example, methanol, suitably at ambient temperature.

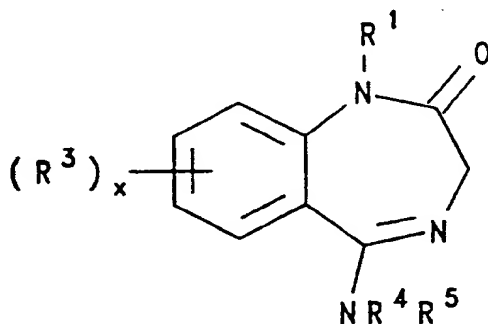
- 30 -

Intermediates of formula (II) wherein  $R^{30}$  is  $-N=C=O$  (hereinafter intermediates (IIB)) may be prepared from amines of formula (IIA) by reaction with triphosgene in the presence of a base, such as a tertiary amine, for example, triethylamine. The reaction is conveniently effected in a suitable organic solvent, such as an ether, for example, tetrahydrofuran, suitably at low temperature, such as about  $0^{\circ}\text{C}$ .

Intermediates of formula (V) may be prepared from intermediates of formula (IV) by reaction with a compound of formula  $R^{50}N=C=O$ , wherein  $R^{50}$  is as previously defined.

The reaction is conveniently effected in a suitable organic solvent, such as an ether, for example, tetrahydrofuran, suitably at elevated temperature, for example, about  $60^{\circ}\text{C}$ .

Intermediates of formula (IV) may be prepared from compounds of formula (VI)



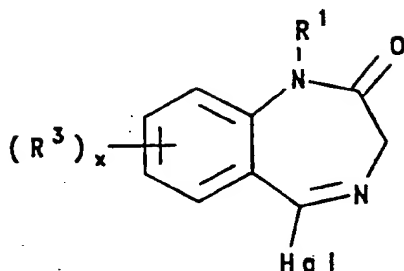
(VI)

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$  and  $x$  are as defined for formula (I), by reaction with isoamyl nitrite in the presence of a base.

Suitable bases of use in the reaction include alkali metal alkoxides, such as potassium *t*-butoxide.

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Compounds of formula (VI) may be prepared from compounds of formula (VII)



(VII)

wherein  $R^1$ ,  $R^3$  and  $x$  are as defined for formula (I) and Hal represents halo, such as chloro, by reaction with an amine of formula  $HNR^4R^5$ .

15                   Compounds of formula (VII) may be prepared as described in United Kingdom Patent Specification no. 1,145,471.

20                   Compounds of formula (III) wherein  $R^{31}$  is  $-N=C=O$  (IIIB) may be prepared from the corresponding compounds of formula (III) wherein  $R^{31}$  is  $NH_2$  (IIIA) analogously to the preparation of compounds of formula (IIB) from compounds of formula (IIA).

25                   Compounds of formula (IIIA) and  $HOC(=O)(CH_2)_sR^{13}$  are commercially available or may be prepared from commercially available starting materials by known methods.

30                   Where the above-described process for the preparation of the compounds according to the invention gives rise to mixtures of stereoisomers these isomers may, if desired, be separated, suitably by conventional techniques such as preparative chromatography.

The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel

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compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-L-tartaric acid and/or (+)-di-p-toluoyl-D-tartaric acid followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, enantiomers of the novel compounds may be separated by HPLC using a chiral column.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following non-limiting examples are provided to assist in a further understanding of the invention.

EXAMPLE 1: N-[3(R,S)-2,3-Dihydro-5-(1,4-dioxo-8-azaspiro  
[4.5]decan-8-yl)-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl]  
N'-[3-methylphenyl] urea

a) 5-(1,4-Dioxo-8-azaspiro[4.5]decan-8-yl)-2-oxo-1-propyl-  
1,4-benzodiazepine

To a solution of 1-propyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione (13.5g) (prepared in the same way as described in Example 4a and b except using N-propylantranilic acid methyl ester as starting material) in dichloromethane (250ml) was added phosphorus pentachloride (15.9g) in dichloromethane (100ml) over 30 min. The reaction mixture was stirred at room temperature for 2h then concentrated under high vacuum. The residue obtained was redissolved in dichloromethane (200ml), cooled to 0°C and 1,4-dioxo-8-azaspiro[4.5]decan-8-yl-2-oxo-1-propyl-1,4-benzodiazepine (24.2ml) in dichloromethane (100ml) was added dropwise. The reaction mixture was allowed to warm to room temperature and left to stir for 14h, washed with saturated sodium carbonate solution (2 x 15ml), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was dissolved in dichloromethane and filtered through a short plug of silica using 20% ethyl acetate in dichloromethane as eluant, then triturated with diethyl ether to give the required compound (18.2g). mp 142°C. <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 0.68 (3H, t, J=7.4Hz), 1.24 (1H, m), 1.38 (1H, m), 1.51 (2H, m), 1.72 (2H, m), 3.25 (4H, m), 3.35 (1H, d, J=11.4Hz), 3.55 (1H, m), 3.88 (4H, s), 3.94 (1H, d, J=11.4Hz), 4.20 (1H, m), 7.31 (1H, m), 7.54 (3H, m). MS (CI) m/e 344 [MH]<sup>+</sup>.

b) 5-(1,4-Dioxo-8-azaspiro[4.5]decan-8-yl)-3-oximido-  
2-oxo-1-propyl-1,4-benzodiazepine

The product from step a) (18g) was dissolved in dry toluene and cooled to -20°C under an atmosphere of nitrogen. Potassium *tert*-butoxide (16.3g) was added and after 20 min isoamyl nitrite (7.72ml) was added dropwise. The reaction

mixture was stirred at -20°C for 14h then allowed to warm to room temperature and quenched with dilute hydrochloric acid to pH 7. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 200ml). The organic layers were combined, dried (MgSO<sub>4</sub>), filtered and concentrated under vacuum. The residue was triturated with diethyl ether to give the required compound (5.27g). mp 197°C. <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 0.71 (3H, 2 x t, J=7.3Hz), 1.24-1.54 (6H, m), 3.04-3.80 (5H, m), 3.91 (4H, s), 4.23 (1H, m), 7.18-7.62 (4H, m), 9.95 and 10.17 (1H, 2 x s). MS (CI) m/e 373 [MH]<sup>+</sup>.

c) N-[3(RS)-2,3-Dihydro-5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl] N'-(3-methylphenyl) urea

The product from step b) (1.5g) was dissolved in methanol (40ml) and 5% rhodium on carbon catalyst (1.5g) was added to the solution. The reaction mixture was heated at 60°C under 50 psi of hydrogen on a Parr apparatus for 6h then cooled, filtered and concentrated under vacuum. The residue was dissolved in dry dichloromethane (40ml) and *m*-tolyl isocyanate (0.5ml) was added in one portion. The reaction mixture was stirred at room temperature for 2h then concentrated under vacuum. The residue was purified by chromatography on silica gel using 65% ethyl acetate in hexane as eluant to give the title compound (0.14g). mp 238-240°C. <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 0.70 (3H, t, J=7.5Hz), 1.26 (1H, m), 1.39 (1H, m), 1.54 (2H, m), 1.73 (2H, m), 2.21 (3H, s), 3.25 (4H, m), 3.64 (1H, m), 3.88 (4H, s), 4.23 (1H, m), 4.92 (1H, d, J=8.4Hz), 6.70 (1H, d, J=6.8Hz), 7.01-7.65 (8H, m), 8.82 (1H, s). MS (CI) m/e 492 [MH]<sup>+</sup>. Anal. Found C, 65.92; H, 6.61; N, 14.27. C<sub>27</sub>H<sub>33</sub>N<sub>5</sub>O<sub>4</sub> requires C, 65.97; H, 6.77; N, 14.25%.



EXAMPLE 2: N-[3(RS)-2,3-Dihydro-2-oxo-5-(4-oxopiperidin-1-yl)-1-propyl-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea

To a solution of the product from Example 1c) (0.1g) in 1,4-dioxan (30ml) was added perchloric acid (3ml). The reaction mixture was stirred at room temperature for 14h then concentrated under high vacuum. The residue was partitioned between ethyl acetate (50ml) and saturated sodium hydrogen carbonate solution (30ml) then the organic layer was dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under vacuum. The crude product was purified by chromatography on silica gel using 65% ethyl acetate in hexane as eluant to give the title compound (0.06g). mp 150-152°C.  $^1\text{H}$  NMR (360MHz,  $\text{D}_6$ -DMSO)  $\delta$  0.70 (3H, t,  $J=7.3\text{Hz}$ ), 1.27 (1H, m), 1.41 (1H, m), 2.22 (3H, s), 2.26 (2H, m), 2.49 (2H, m), 3.52 (4H, m), 3.64 (1H, m), 4.23 (1H, m), 4.97 (1H, d,  $J=8.4\text{Hz}$ ), 6.71 (1H, d,  $J=7.2\text{Hz}$ ), 7.10 (3H, m), 7.17 (1H, s), 7.42 (1H, m), 7.68 (3H, m), 8.83 (1H, s). MS (CI)  $m/e$  448  $[\text{MH}]^+$ . Anal. Found C, 65.45; H, 6.49; N, 15.09.  $\text{C}_{25}\text{H}_{29}\text{N}_5\text{O}_3 \cdot 0.6\text{H}_2\text{O}$  requires C, 65.51; H, 6.64; N, 15.28%.

EXAMPLE 3: N-[3(RS)-2,3-Dihydro-2-oxo-1-propyl-5-(4-[1,1,1-trifluoroethylaminel]piperidin-1-yl)-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea

The product from Example 2 (0.5g) was dissolved in methanol (50ml) with trifluoroethylamine hydrochloride (0.272g). Crushed 3Å sieves (10g) were added to the mixture, followed by sodium cyanoborohydride (0.087g). Methanolic hydrogen chloride was added dropwise until a pH of 5 was attained and stirring was continued at room temperature for 4 days. The reaction mixture was filtered and the solvent was removed under vacuum. The residue was dissolved in ethyl acetate and washed with saturated sodium hydrogen carbonate solution. The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ), filtered and

concentrated *in vacuo*. The solid obtained was recrystallised from ethyl acetate/hexane to give the title compound (0.16g). mp 209-210°C. <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 0.70 (3H, t, J=7.3Hz), 1.14-1.45 (4H, m), 1.73-1.85 (2H, m), 2.21 (3H, s), 2.35 (1H, m, disappears on D<sub>2</sub>O shake), 2.65-2.83 (3H, m), 3.22 (2H, m), 3.60-3.67 (3H, m), 4.23 (1H, m), 4.92 (1H, d, J=8.4Hz), 6.70 (1H, d, J=6.8Hz), 6.99-7.12 (4H, m), 7.38 (1H, m), 7.54 (1H, d, J=7.6Hz), 7.64 (2H, m), 8.81 (1H, s). MS (CI) m/e 531 [MH]<sup>+</sup>. Anal. Found C, 61.48; H, 6.18; N, 15.82. C<sub>27</sub>H<sub>33</sub>F<sub>3</sub>O<sub>2</sub> requires C, 61.12; H, 6.27; N, 15.84%.

EXAMPLE 4: N-[3(R,S)-2,3-Dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[indan-5-yl] urea

Intermediate 1: 4,4-Dimethylpiperidine

To a solution of lithium aluminium hydride in diethyl ether (430ml of a 1.0M solution) under nitrogen, at reflux, was added a suspension of 3,3-dimethylglutarimide (20g) in anhydrous diethyl ether (570ml), dropwise over a period of 1h. The mixture was then heated at reflux for a further 8h then cooled to 0°C. Water (16ml) was added dropwise, followed by aqueous sodium hydroxide (16ml of a 4N solution) and water (48ml). The resultant solid was removed by filtration, the filtrate dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The pale yellow oil was distilled under reduced pressure to afford the title piperidine (12.3g). bp 44°C/25mmHg. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 0.93 (6H, s), 1.29-1.32 (4H, m), 2.78-2.81 (4H, m).

a) Methyl 2-(N-bromoacetyl-N-methylamino)benzoate

A solution of bromoacetyl bromide (209g) in dichloromethane (200ml) was added dropwise to a cooled (ice bath) solution of methyl N-methylantranilate (168g) in dichloromethane (1.4l). A solution of sodium hydroxide (59g) in water (400ml) was added dropwise and the reaction mixture was

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stirred at room temperature for 20h. The organic phase was separated and washed with 1M hydrochloric acid (500ml), brine (300ml), saturated sodium hydrogen carbonate solution (400ml), dried ( $\text{Na}_2\text{SO}_4$ ) then evaporated to afford the required product (255g).  $^1\text{H}$  NMR (360MHz,  $\text{CDCl}_3$ )  $\delta$  3.23 (3H, s), 3.54 (1H, d,  $J=11\text{Hz}$ ), 3.60 (1H, d,  $J=11\text{Hz}$ ), 3.90 (3H, s), 7.40 (1H, d,  $J=8\text{Hz}$ ), 7.51 (1H, dd,  $J_1 = J_2 = 8\text{Hz}$ ), 7.65 (1H, dd,  $J_1 = J_2 = 8\text{Hz}$ ), 8.04 (1H, d,  $J=8\text{Hz}$ ).

b) 1-Methyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione

Ammonia gas was bubbled through an ice-cooled solution of methyl 2-(N-bromoacetyl-N-methylamino)benzoate (255g) in methanol (1600ml) until saturated. The cooling bath was removed and the reaction mixture left standing at room temperature for 18h. The precipitate was collected to afford the required product (79g). mp 190-193°C.  $^1\text{H}$  NMR (360MHz,  $\text{CDCl}_3$ )  $\delta$  3.42 (3H, s), 3.80 (2H, brs), 6.80 (1H, s), 7.24 (1H, d,  $J=8\text{Hz}$ ), 7.32 (1H, dd,  $J_1 = J_2 = 8\text{Hz}$ ), 7.57 (1H, dd,  $J_1 = J_2 = 8\text{Hz}$ ), 7.90 (1H, d,  $J=8\text{Hz}$ ). Found: C, 63.20; H, 5.25; N, 14.77.  $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2$  requires C, 63.15; H, 5.30; N, 14.73%.

c) 1,2-Dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-3H-1,4-benzodiazepin-2-one

To a solution of the product of part b) (10g) in anhydrous dichloromethane (700ml) was added phosphorus pentachloride (13.17g) in anhydrous dichloromethane (500ml) over a period of 30 min. The reaction mixture was stirred at ambient temperature for 2.5h. The solvent was evaporated *in vacuo* and the residue redissolved in anhydrous dichloromethane (400ml). After cooling to 0°C, a solution of 4,4-dimethylpiperidine (Intermediate 1) (5.95g) and triethylamine (18.3ml) in anhydrous dichloromethane (100ml) was added dropwise. The reaction mixture was allowed to warm to ambient temperature with stirring for 19h, washed with saturated potassium carbonate solution (500ml), water (200ml) and brine (150ml).

The organic layer was dried ( $K_2CO_3$ ) and treated with decolourising charcoal and silica gel. After filtering, the solvent was evaporated *in vacuo*. The residue was redissolved in dichloromethane (300ml) and extracted with citric acid solution (10%, 3 x 50ml). The combined aqueous layers were basified (4M NaOH solution) and extracted with dichloromethane (6 x 125ml). These organic extracts were combined, dried ( $K_2CO_3$ ) and evaporated *in vacuo* to give the title compound (7.5g). mp 143-145°C.  $^1H$  NMR (360MHz,  $CDCl_3$ )  $\delta$  0.98 (6H, s), 1.26-1.36 (2H, m), 1.46-1.53 (2H, m), 3.13-3.32 (4H, m), 3.36 (3H, s), 3.50 (1H, d,  $J=12.0Hz$ ), 4.24 (1H, d,  $J=12.0Hz$ ), 7.21 (1H, t,  $J=8.3Hz$ ), 7.27 (1H, d,  $J=8.3Hz$ ), 7.46-7.53 (2H, m). MS (CI)  $m/e$  286  $[MH]^+$ .

d) 1,2-Dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-3-oximido-3H-1,4-benzodiazepin-2-one

A solution of the product of part c) (7g) in anhydrous toluene (200ml) was cooled to -20°C under an atmosphere of nitrogen, and potassium *tert*-butoxide (7.5g) was added portionwise over 5 min. After stirring at -20°C for 30 min, isopentyl nitrite (3.9ml) was added dropwise. The reaction mixture was stirred at -20°C for 5h 30 min and then allowed to warm to ambient temperature. The mixture was poured onto a rapidly stirred mixture of ethyl acetate (300ml) and water (50ml) containing citric acid (4.68g), stirred vigorously for 5 min and then neutralised to pH 7 using saturated potassium carbonate solution. The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 x 100ml). The combined organic phases were dried ( $Na_2SO_4$ ) and evaporated *in vacuo* to give an orange solid. This was triturated with diethyl ether to give the title compound (6.92g). mp 215°C (dec.).  $^1H$  NMR (360MHz,  $D_6$ -DMSO)  $\delta$  0.97 (6H, s), 1.23-1.36 (2H, m), 1.40-1.50 (2H, m), 3.22-3.50 (7H, m), 7.26-7.32 (1H, m), 7.44 (1H, d,  $J=7.9Hz$ ), 7.48-7.60 (2H, m), 10.10 (1H, brs). MS (CI)  $m/e$  315  $[MH]^+$ .

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e) 1,2-Dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-3-(O-ethylaminocarbonyl)oximido-3H-1,4-benzodiazepin-2-one

To a suspension of the product of part d) (3.64g) in anhydrous tetrahydrofuran (60ml) was added triethylamine (1.6ml) followed by ethyl isocyanate (1.4ml) dropwise. This mixture was heated at 60°C under an atmosphere of nitrogen for 3h. The solvent was evaporated *in vacuo* and the residue chromatographed on silica gel using a gradient of 0% to 3% methanol in dichloromethane as eluant to give the title compound (4.5g). <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.02 (6H, brs), 1.13 (3H, t, J=7.3Hz), 1.20-1.84 (4H, m), 3.20-3.30 (3H, m), 3.35-3.42 (4H, m), 3.60-3.78 (1H, m), 3.80-4.00 (1H, m), 6.36-6.42 (1H, m), 7.20-7.35 (3H, m), 7.46-7.52 (1H, m). MS (CI) m/e 386 [MH]<sup>+</sup>.

f) N-[3(R,S)-2,3-Dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-indan-5-yl urea

To a solution of the product of part e) (4.5g) in methanol (250ml) was added 10% palladium on carbon (1g). The mixture was hydrogenated at 40 psi for 3h and then the catalyst was filtered off and washed with methanol. The solvent was evaporated *in vacuo* to give the amine (3.5g) which was used without further purification.

To a solution of 5-aminoindane (2.32g) in anhydrous tetrahydrofuran (150ml) cooled to 0°C under an atmosphere of nitrogen was added triphosgene (1.72g) in one portion. Triethylamine (7.2ml) was added dropwise. After stirring at 0°C for 30 min a solution of the amine (3.5g) in anhydrous tetrahydrofuran (20ml) was added dropwise. The mixture was stirred at 0°C for 5 min and then was allowed to warm to ambient temperature and stirred for 10 min. The solvent was evaporated *in vacuo* and the residue partitioned between ethyl acetate (150ml) and water (75ml). The undissolved solid was collected by filtration to afford the title product (3.17g). mp

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132°C (dec.). <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 0.96 (6H, s), 1.30-1.39 (2H, m), 1.44-1.56 (2H, m), 2.04 (2H, quin, J=7.4Hz), 2.84 (4H, q, J=7.0Hz), 3.16-3.26 (2H, m), 3.28-3.38 (2H, m), 3.42 (3H, s), 5.32 (1H, d, J=8.0Hz), 6.59-6.66 (1H, m), 6.95-7.13 (3H, m), 7.24-7.36 (3H, m), 7.51-7.58 (2H, m). MS (CI) m/e 460 [MH]<sup>+</sup>. Anal. Found C, 67.85; H, 7.11; N, 14.60. C<sub>27</sub>H<sub>33</sub>N<sub>5</sub>O<sub>2</sub>·H<sub>2</sub>O requires C, 67.90; H, 7.39; N, 14.66%.

An alternative procedure can be used for preparation of N-[3(R,S)-2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-indan-5-yl] urea:

**Step 1: Indan-5-yl isocyanate**

To a solution of 5-aminoindane (25g) in anhydrous diethyl ether (1250ml), under an atmosphere of nitrogen, at 0°C was added triphosgene (18.3g). The mixture was stirred at 0°C for 2 min then triethylamine (64.7ml) was added until pH8. The mixture was stirred at 0°C for 10 min then at 10°C for 10 min. The undissolved solids were filtered off and the filtrate evaporated *in vacuo*. The residue was distilled at 100°C/1mbar to afford the title compound (20g). <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 2.07 (2H, quin, J=7.5Hz), 2.86 (4H, m), 6.84 (1H, dd, J=7.9 and 2.0Hz), 6.94 (1H, s), 7.13 (1H, d, J=7.9Hz).

**Step 2: N-[3(R,S)-2,3-Dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]N'-[indan-5-yl] urea**

To a solution of 1,2-dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-3-(O-ethylaminocarbonyl)oximido-3H-1,4-benzodiazepin-2-one (10.3g) in methanol (400ml) was added 10% palladium on carbon (2.24g, 21% (w/w)). The mixture was hydrogenated at 40 psi for 4h then the catalyst was filtered off and washed with methanol. The solvent was evaporated *in vacuo* to give the crude amine (8.3g).

To a stirred solution of the crude amine (8.3g) in anhydrous diethyl ether (50ml) under an atmosphere of

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nitrogen, at room temperature, was added a solution of indan-5-yl isocyanate (4.2g) in anhydrous diethyl ether (7ml). After stirring at room temperature for 10 min the title compound (8.9g) was collected by filtration.

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EXAMPLE 5: Chiral Separation of N-[3(R,S)-2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[indan-5-yl] urea

10 N-[3(R,S)-2,3-Dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[indan-5-yl] urea (0.17g) was dissolved in 1:1 chloroform:methanol (4ml). 440µl of this solution was injected onto a dinitrobenzoyl leucine column (250 x 20mm i.d., 5µm) per run using 95:5:1 1-chlorobutane:methanol:acetic acid as the mobile phase. Using  
15 a flow rate of 20ml/min and UV detection at 330nm, the two enantiomers were efficiently separated. The fractions containing each separate enantiomer were combined and evaporated *in vacuo*. Separately each enantiomer was partitioned between ethyl acetate (25ml) and potassium carbonate solution (0.5M, 10ml). The organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated  
20 *in vacuo*. The residues obtained were redissolved in dichloromethane and saturated ethereal hydrogen chloride (~ 2ml) was added. The solvents were evaporated *in vacuo* and the residues obtained were triturated with diethyl ether and the  
25 resulting solids collected by filtration to give:

Peak A (69mg). mp 180°C (dec.). <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 0.92-1.06 (6H, m), 1.22-1.62 (4H, m), 1.97 (2H, quin, J=7.3Hz), 2.77 (4H, q, J=7.3Hz), 3.23-3.70 (7H, m), 5.30-5.38 (1H, m), 7.05-7.13 (2H, m), 7.29 (2H, brs), 7.56 (1H, t, J=7.5Hz), 7.71 (1H, d, J=8.2Hz), 7.83-7.92 (2H, m), 9.93 (1H, brs), 10.56 (1H, brs). MS (CI) m/e 460 [MH]<sup>+</sup>. Anal. Found C, 61.67; H, 6.81; N, 13.67. C<sub>27</sub>H<sub>33</sub>N<sub>5</sub>O<sub>2</sub>.HCl.1.5(H<sub>2</sub>O) requires C, 61.67; H, 6.81; N, 13.67.

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62.00; H, 7.13; N, 13.39%.  $[\alpha]_D^{22}$  -241.1° (c=0.54, MeOH). Purity A:B = > 99.5:0.5.

5 Peak B (67mg). mp 180°C (dec.).  $^1\text{H}$  NMR (360MHz,  $\text{D}_6$ -DMSO)  $\delta$  0.92-1.06 (6H, m), 1.22-1.62 (4H, m), 1.97 (2H, quin,  $J=7.3\text{Hz}$ ), 2.77 (4H, q,  $J=7.3\text{Hz}$ ), 3.23-3.70 (7H, m), 5.30-5.38 (1H, m), 7.05-7.13 (2H, m), 7.28 (2H, brs), 7.56 (1H, t,  $J=7.5\text{Hz}$ ), 7.71 (1H, d,  $J=8.2\text{Hz}$ ), 7.83-7.92 (2H, m), 9.33 (1H, brs), 10.46 (1H, brs). MS (CI)  $m/e$  460  $[\text{MH}]^+$ . Anal. Found C, 61.49; H, 7.06; N, 13.39.  $\text{C}_{27}\text{H}_{33}\text{N}_5\text{O}_2 \cdot \text{HCl} \cdot 1.75(\text{H}_2\text{O})$  requires C, 10 61.47; H, 7.16; N, 13.27%.  $[\alpha]_D^{26}$  +226.8° (c=0.63, MeOH). Purity A:B = 1.7:98.3.

15 EXAMPLE 6: N-[3(R,S)-2,3-Dihydro-5-(cis-2,6-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-(3-methylphenyl) urea

a) 1,2-Dihydro-5-(cis-2,6-dimethylpiperidin-1-yl)-1-methyl-3-oximido-3H-1,4-benzodiazepin-2-one

20 Prepared as in Example 4, steps c) and d), from 1-methyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione (5g) and *cis*-2,6-dimethylpiperidine (3.5ml). mp 240°C (dec.).  $^1\text{H}$  NMR (360MHz,  $\text{D}_6$ -DMSO)  $\delta$  0.85-0.96 (3H, m), 1.20-1.92 (9H, m), 3.31 (3H, s), 3.97-4.09 (1H, m), 4.36-4.56 (1H, m), 7.25-7.34 (1H, m), 7.40 (1H, d,  $J=7.7\text{Hz}$ ), 7.49-7.60 (2H, m), 9.88-10.16 (1H, m). MS (CI)  $m/e$  315  $[\text{MH}]^+$ .

25 b) N-[3(R,S)-2,3-Dihydro-5-(cis-2,6-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-(3-methylphenyl) urea

30 To a suspension of the product of part a) (1.5g) in methanol (150ml) was added 5% rhodium on carbon (1.5g, 100% (w/w)). The mixture was hydrogenated at 40 psi at 60°C for 6h 30min and, after cooling, the catalyst was filtered off and washed with methanol. The solvent was evaporated *in vacuo* to give the amine (1.43g).



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The amine was redissolved in anhydrous tetrahydrofuran (20ml) and cooled to 0°C under an atmosphere of nitrogen. *m*-Tolyl isocyanate (0.62ml) was added dropwise. After stirring for 10 min the mixture was left standing in the fridge overnight.

5 The reaction mixture was evaporated *in vacuo* and the residue partitioned between ethyl acetate (50ml) and water (30ml). The aqueous layer was separated and extracted with ethyl acetate (25ml). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated *in vacuo*. The residue was chromatographed on silica  
10 gel using a gradient of 0% to 50% ethyl acetate in dichloromethane as the eluant to afford a gum. This was further purified by chromatographing on silica gel using 20% ethyl acetate in dichloromethane as the eluant to afford a solid. This was triturated with diethyl ether to give the title compound  
15 (0.32g). mp 248°C (dec.). <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 0.88-1.03 (3H, m), 1.33 (3H, d, J=6.9Hz), 1.42-1.90 (6H, m), 2.28 (3H, s), 3.42 (3H, s), 3.90-4.32 (2H, m), 5.27 (1H, d, J=8.0Hz), 6.42-6.50 (1H, m), 6.81 (1H, d, J=7.0Hz), 6.91 (1H, brs), 7.06-7.16 (2H, m), 7.21-7.28 (2H, m), 7.32 (1H, d, J=7.8Hz), 7.42-7.52 (2H, m). MS  
20 (CI) m/e 434 [MH]<sup>+</sup>. Anal: Found C, 68.07; H, 7.12; N, 15.98. C<sub>23</sub>H<sub>31</sub>N<sub>5</sub>O<sub>2</sub>·0.35(H<sub>2</sub>O) requires C, 68.27; H, 7.26; N, 15.92%.

EXAMPLE 7: N-[3(R,S)-2,3-Dihydro-1-methyl-5-(4-methylpiperidin-1-yl)-2-oxo-1H-1,4-benzodiazepin-3-yl]  
25 N'-[3-methylphenyl] urea

a) 1,2-Dihydro-1-methyl-5-(4-methylpiperidin-1-yl)-3-oximido-3H-1,4-benzodiazepin-2-one

Prepared as in Example 4, steps c) and d) from 1-methyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione (5g) and 4-methylpiperidine (10.9ml). mp 225-228°C. <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 0.90-1.15 (4H, m), 1.20-1.36 (1H, m), 1.54-1.76 (3H, m), 2.77-3.01 (2H, m), 3.26 (3H, s), 3.69-4.24 (2H, m), 7.24-7.32

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(1H, m), 7.38-7.43 (1H, m), 7.46-7.58 (2H, m), 9.93 and 10.16 (1H, 2 x s). MS (CI) m/e 301 [MH]<sup>+</sup>.

b) N-[3(R,S)-2,3-Dihydro-1-methyl-5-(4-methylpiperidin-1-yl)-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea

In the same way as in Example 6b) from 1,2-dihydro-1-methyl-5-(4-methylpiperidin-1-yl)-3-oximido-3H-1,4-benzodiazepin-2-one (0.6g), the amine (0.57g) was obtained. The title compound was then prepared from the crude amine and *m*-tolyl isocyanate (0.26ml) as described in Example 6b) and recrystallised from methanol. mp 142°C (dec.). <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 0.95 (3H, d, J=6.3Hz), 1.06-1.19 (1H, m), 1.24-1.36 (1H, m), 1.46-1.60 (2H, m), 1.65-1.76 (1H, m), 2.28 (3H, s), 2.62-2.82 (2H, m), 3.41 (3H, s), 3.48-3.58 (1H, m), 3.90-3.98 (1H, m), 5.28 (1H, d, J=8.6Hz), 6.54 (1H, d, J=7.9Hz), 6.82 (1H, d, J=7.3Hz), 6.95 (1H, s), 7.04-7.16 (2H, m), 7.21-7.32 (3H, m), 7.45-7.56 (2H, m). MS (CI) m/e 420 [MH]<sup>+</sup>. Anal. Found C, 65.09; H, 6.79; N, 15.94. C<sub>24</sub>H<sub>29</sub>N<sub>5</sub>O<sub>2</sub>·1.25(H<sub>2</sub>O) requires C, 65.21; H, 7.18; N, 15.84%.

EXAMPLE 8: Chiral separation of N-[3(R,S)-2,3-dihydro-1-methyl-5-(4-methylpiperidin-1-yl)-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea

N-[3(R,S)-2,3-Dihydro-1-methyl-5-(4-methylpiperidin-1-yl)-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea (0.6g) was dissolved in 1:24 methanol:dichloromethane (6ml). The enantiomers were separated as described in Example 5. Peak A (250mg). mp 178°C (dec.). <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 0.96-1.08 (3H, m), 1.30-1.44 and 1.64-1.86 (4H, 2 x m), 1.95-2.06 (1H, m), 2.28 (3H, s), 3.14-3.60 (5H, m), 3.62-3.76 (1H, m), 4.32-4.42 and 4.64-4.70 (1H, 2 x m), 5.67-5.76 (1H, m), 6.80 (1H, d, J=7.4Hz), 7.11 (1H, t, J=7.8Hz), 7.16-7.34 (3H, m), 7.38-7.64

(3H, m), 7.72-7.82 (1H, m), 8.07 and 8.50 (1H, 2 x brs), 11.85 and 11.96 (1H, 2 x brs). MS (CI) m/e 420 [MH]<sup>+</sup>.

$[\alpha]_D^{23}$  -247.7° (c=0.50, MeOH). Purity A:B = > 99.5:0.5.

5 Peak B (270mg). mp 180°C (dec.). <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 0.96-1.08 (3H, m), 1.30-1.44 and 1.64-1.86 (4H, 2 x m), 1.95-2.06 (1H, m), 2.28 (3H, s), 3.14-3.60 (5H, m), 3.62-3.76 (1H, m), 4.32-4.42 and 4.64-4.70 (1H, 2 x m), 5.67-5.76 (1H, m), 6.80 (1H, d, J=7.4Hz), 7.11 (1H, t, J=7.8Hz), 7.16-7.34 (3H, m), 7.38-7.64 (3H, m), 7.72-7.82 (1H, m), 8.07 and 8.50 (1H, 2 x brs),  
10 11.85 and 11.96 (1H, 2 x brs). MS (CI) m/e 420 [MH]<sup>+</sup>.  $[\alpha]_D^{23}$  +244.3° (c=0.50, MeOH). Purity A:B = 2.3:97.7.

EXAMPLE 9: N-[3(R,S)-2,3-Dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]

15 N'-[3-methylphenyl] urea

The amine was prepared as in Example 6b), from 1,2-dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-3-oximido-3H-1,4-benzodiazepin-2-one (7.5g). The title compound was prepared from the crude amine and *m*-tolyl isocyanate (3.1ml) as  
20 described in Example 6b). mp 135°C (dec.). <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 0.95 (6H, s), 1.28-1.38 (2H, m), 1.44-1.51 (2H, m), 2.26 (3H, s), 3.15-3.24 (2H, m), 3.26-3.39 (2H, m), 3.43 (3H, s), 5.33 (1H, d, J=8.0Hz), 6.65-6.72 (1H, m), 6.82 (1H, d, J=7.0Hz), 7.06-7.19 (3H, m), 7.22-7.35 (3H, m), 7.50-7.57 (2H, m). MS (CI)  
25 m/e 434 [MH]<sup>+</sup>. Anal. Found C, 66.76; H, 7.03; N, 15.60. C<sub>25</sub>H<sub>31</sub>N<sub>5</sub>O<sub>2</sub>·0.9(H<sub>2</sub>O) requires C, 66.76; H, 7.03; N, 15.57%.

EXAMPLE 10: Chiral Separation of N-[3(R,S)-2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea

30 N-[3(R,S)-2,3-Dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea (0.27g) was dissolved in 2:3 methanol:dichloromethane

(5ml). The enantiomers were separated as described in Example 5.

Peak A (103mg). mp 170°C (dec.). <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 0.92-1.07 (6H, m), 1.27-1.40 (1H, m), 1.49-1.65 (3H, m), 2.23 (3H, s), 3.30-3.77 (7H, m), 5.30-5.38 (1H, m), 6.76 (1H, d, J=7.3Hz), 7.08-7.19 (2H, m), 7.23 (1H, s), 7.32-7.39 (1H, m), 7.56 (1H, t, J=7.6Hz), 7.71 (1H, d, J=8.1Hz), 7.82-7.92 (2H, m), 9.50 (1H, brs), 10.57 (1H, brs). MS (CI) m/e 434 [MH]<sup>+</sup>. Anal. Found C, 62.00; H, 7.09; N, 14.11. C<sub>25</sub>H<sub>31</sub>N<sub>5</sub>O<sub>2</sub>·HCl·0.8(H<sub>2</sub>O) requires C, 61.99; H, 6.99; N, 14.46%. [α]<sub>D</sub><sup>22</sup> -264.9° (c=0.61, MeOH). Purity A:B = > 99.5:0.5.

Peak B (89mg). mp 172°C (dec.). <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 0.92-1.05 (6H, m), 1.25-1.40 (1H, m), 1.45-1.65 (3H, m), 2.23 (3H, s), 3.16-3.76 (7H, m), 5.26-5.37 (1H, m), 6.76 (1H, d, J=7.2Hz), 7.06-7.36 (4H, m), 7.50-7.60 (1H, m), 7.67-7.74 (1H, m), 7.78-7.94 (2H, m), 9.40 (1H, brs), 10.46 (1H, brs). MS (CI) m/e 434 [MH]<sup>+</sup>. Anal. Found C, 61.83; H, 7.07; N, 14.03. C<sub>25</sub>H<sub>31</sub>N<sub>5</sub>O<sub>2</sub>·HCl·H<sub>2</sub>O requires C, 61.53; H, 7.02; N, 14.35%. [α]<sub>D</sub><sup>22</sup> +216.6° (c=0.65, MeOH). Purity A:B = 3.0:97.0.

EXAMPLE 11: N-[3(R,S)-2,3-Dihydro-5-(4-methoxypiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]  
N'-[3-methylphenyl] urea

a) 1,2-Dihydro-5-(4-methoxypiperidin-1-yl)-3H-1-methyl-1,4-benzodiazepin-2-one

Prepared as described in Example 4c), from 1-methyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione (4.5g) and 4-methoxypiperidine hydrochloride (3.6g). <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.43-1.86 (3H, m), 1.98-2.08 (1H, m), 2.91-3.18 (2H, m), 3.33-3.60 (9H, m), 3.63-3.75 (1H, m), 4.25-4.31 (1H, m), 7.20-7.32 (2H, m), 7.47-7.53 (2H, m). MS (CI) m/e 288 [MH]<sup>+</sup>.

b) 1,2-Dihydro-5-(4-methoxypiperidin-1-yl)-1-methyl-3-oximido-3H-1,4-benzodiazepin-2-one

Prepared as Example 4d), from 1,2-dihydro-5-(4-methoxypiperidin-1-yl)-methyl-3H-1,4-benzodiazepin-2-one (2.3g) mp 176°C (dec.). <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 1.29-1.50 (1H, m), 1.53-1.65 (1H, m), 1.76-1.88 (1H, m), 1.90-2.04 (1H, m), 3.05-3.95 (11H, m), 7.25-7.32 (1H, m), 7.41-7.63 (3H, m), 9.97 and 10.21 (1H, 2 x brs). MS (CI) m/e 317 [MH]<sup>+</sup>.

c) N-[3(R,S)-2,3-Dihydro-5-(4-methoxypiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea

By the method of Example 6b), from 1,2-dihydro-5-(4-methoxypiperidin-1-yl)-1-methyl-3-oximido-3H-1,4-benzodiazepin-2-one (1.4g) was obtained the amine. The title compound was prepared from the crude amine and *m*-tolyl isocyanate (0.57ml) as described in Example 6b). mp 145-148°C. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>), δ 1.45-1.58 (1H, m), 1.60-1.72 (1H, m), 1.74-1.80 (1H, m), 1.92-2.05 (1H, m), 2.28 (3H, s), 2.97-3.10 (2H, m), 3.30-3.55 (8H, m), 3.64-3.78 (1H, m), 5.33 (1H, d, J=8.0Hz), 6.65-6.75 (1H, m), 6.82 (1H, d, J=6.7Hz), 7.03-7.36 (6H, m), 7.49-7.58 (2H, m). MS (CI) m/e 436 [MH]<sup>+</sup>. Anal. Found C, 62.94; H, 6.63; N, 15.40. C<sub>24</sub>H<sub>29</sub>N<sub>5</sub>O<sub>3</sub>·1.25(H<sub>2</sub>O) requires C, 62.93; H, 6.93; N, 15.29%.

EXAMPLE 12: (-)-N-[2,3-Dihydro-1-methyl-5-(4-methylpiperidin-1-yl)-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[indan-5-yl] urea hydrochloride

The amine was prepared by the method of Example 6b), using 1,2-dihydro-1-methyl-5-(4-methylpiperidin-1-yl)-3-oximido-3H-1,4-benzodiazepin-2-one (5.7g). To a solution of 5-aminoindane (2.53g) in anhydrous tetrahydrofuran (120ml), cooled to 0°C under an atmosphere of nitrogen, was added triphosgene (1.88g) in one portion. Triethylamine (5.3ml) was

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added dropwise. After stirring at 0°C for 20 min, a solution of the amine (5.4g) in anhydrous tetrahydrofuran (20ml) was added dropwise. The mixture was stirred at 0°C for 10 min and then left to stand in the fridge overnight. The reaction mixture was evaporated *in vacuo* and the residue partitioned between ethyl acetate (100ml) and water (50ml). The aqueous layer was separated and extracted with ethyl acetate (50ml). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated *in vacuo*. The residue was triturated with dichloromethane to give N-[3(R,S)-2,3-dihydro-1-methyl-5-(4-methylpiperidin-1-yl)-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[indan-5-yl] urea (2.44g).

The title compound was separated following the procedure of Example 5. mp 185°C (dec). <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 0.87-1.04 (3H, m), 1.20-1.88 (5H, m), 1.97 (2H, quin, J=7.4Hz), 2.77 (4H, q, J=7.3Hz), 3.08-3.62 (6H, m), 3.87-4.20 (1H, m), 5.26-5.38 (1H, m), 7.02-7.11 (2H, m), 7.20-7.33 (2H, m), 7.50-7.58 (1H, m), 7.65-7.72 (1H, m), 7.75-7.93 (2H, m), 9.40 (1H, brs), 10.52 (1H, brs). MS (CI) m/e 446 [MH]<sup>+</sup>. Anal. Found C, 62.51; H, 6.93; N, 13.91. C<sub>26</sub>H<sub>31</sub>N<sub>5</sub>O<sub>2</sub>·HCl·H<sub>2</sub>O requires C, 62.45; H, 6.85; N, 14.01%. [α]<sub>D</sub><sup>22</sup> -245.4° (c=0.62, MeOH). Purity A:B = 99.0:1.0.

EXAMPLE 13: N-[3(R,S)-2,3-Dihydro-5-(cis-2,6-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[indan-5-yl] urea

a) 1,2-Dihydro-5-(cis-2,6-dimethylpiperidin-1-yl)-1-methyl-3-(O-ethylaminocarbonyl)oximido-3H-1,4-benzodiazepin-2-one

Prepared as described in Example 4e), from 1,2-dihydro-5-(cis-2,6-dimethylpiperidin-1-yl)-1-methyl-3-oximido-3H-1,4-benzodiazepin-2-one (1.15g) and ethyl isocyanate (0.43ml). <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.01 (3H, d, J=7.1Hz), 1.12 (3H, t, J=7.2Hz), 1.36 (3H, d, J=7.0Hz), 1.37-1.94 (6H, m),

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3.20-3.31 (2H, m), 3.44 and 3.46 (3H, 2 x s), 4.14-4.23 (1H, m), 4.58-4.67 and 4.72-4.80 (1H, 2 x m), 6.12-6.19 and 6.38-6.46 (1H, 2 x m), 7.20-7.38 (3H, m), 7.43-7.50 (1H, m). MS (CI) m/e 386 (MH)<sup>+</sup>.

5        b) N-[3(R,S)-2,3-Dihydro-5-(cis-2,6-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[indan-5-yl] urea

10        The amine was prepared as in Example 4 f), from 1,2-dihydro-5-(cis-2,6-dimethylpiperidin-1-yl)-1-methyl-3-(O-ethylaminocarbonyl)oximido-3H-1,4-benzodiazepin-2-one (1.41g).

15        The title compound was then prepared from the crude amine (1.1g) and 5-aminoindane (0.73g) as described in Example 4f). mp 240°C (dec.). <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 0.84-0.94 (3H, m), 1.25 (3H, d, J=6.8Hz), 1.40-1.84 (6H, m), 1.96 (2H, quin, J=7.4Hz), 2.75 (4H, q, J=7.0Hz), 3.33 (3H, s), 3.80-4.14 (2H, m), 4.93 (1H, d, J=8.6Hz), 6.88 (1H, d, J=8.5Hz), 7.03 (2H, s), 7.29 (1H, s), 7.33-7.39 (1H, m), 7.48 (1H, d, J=8.0Hz), 7.54-7.64 (2H, m), 8.74 (1H, s). MS (CI) m/e 460 [MH]<sup>+</sup>. Anal. Found C, 69.83; 20        H, 7.15; N, 14.82. C<sub>27</sub>H<sub>33</sub>N<sub>5</sub>O<sub>2</sub>·0.25(H<sub>2</sub>O) requires C, 69.88; H, 7.28; N, 15.09%.

25        EXAMPLE 14: Chiral Separation of N-[3(R,S)-2,3-dihydro-5-(4-methoxypiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea.

30        N-[3(R,S)-2,3-Dihydro-5-(4-methoxypiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea (Example 11) (0.32g) was dissolved in 4:1 chloroform:methanol (4ml). The enantiomers were separated as described in Example 5.

Peak A (135mg). mp 165°C (dec.). <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 1.42-1.60 (1H, m), 1.63-1.87 (2H, m), 1.94-2.08 (1H, m), 2.23 (3H, s), 3.14-3.86 (11H, m), 5.26-5.38 (1H, m), 6.76 (1H,

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d,  $J=7.0\text{Hz}$ ), 7.08-7.17 (2H, m), 7.22 (1H, brs), 7.28-7.38 (1H, m), 7.50-7.59 (1H, m), 7.70 (1H, d,  $J=8.5\text{Hz}$ ), 7.78-7.83 (1H, m), 9.39 (1H, brs), 10.54 (1H, brs). MS (CI)  $m/e$  436  $[\text{MH}]^+$ .  $[\alpha]_D^{25} -265.2^\circ$  ( $c=0.16$ , MeOH). Purity A:B = > 99.5:0.5.

5        Peak B (125mg). mp  $165^\circ\text{C}$  (dec.).  $^1\text{H}$  NMR (360MHz,  $\text{D}_6$ -DMSO)  $\delta$  1.42-1.60 (1H, m), 1.63-1.87 (2H, m), 1.94-2.08 (1H, m), 2.23 (3H, s), 3.14-3.86 (11H, m), 5.26-5.38 (1H, m), 6.76 (1H, d,  $J=7.0\text{Hz}$ ), 7.08-7.17 (2H, m), 7.22 (1H, brs), 7.28-7.38 (1H, m), 7.50-7.59 (1H, m), 7.70 (1H, d,  $J=8.5\text{Hz}$ ), 7.78-7.83 (1H, m), 9.41  
10        (1H, brs), 10.54 (1H, brs). MS (CI)  $m/e$  436  $[\text{MH}]^+$ .  $[\alpha]_D^{25} +244.2^\circ$  ( $c=0.18$ , MeOH). Purity A:B = 1:99.

15        EXAMPLE 15: Chiral Separation of N-[3(R,S)-2,3-dihydro-5-(cis-2,6-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[indan-5-yl] urea.

20        N-[3(R,S)-2,3-Dihydro-5-(cis-2,6-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[indan-5-yl] urea (Example 13) (0.95g) was dissolved in 3:1 chloroform:methanol (20ml). The enantiomers were separated as described in Example 5.

25        Peak A (0.44g). mp  $160^\circ\text{C}$  (dec.).  $^1\text{H}$  NMR (360MHz,  $\text{D}_6$ -DMSO)  $\delta$  0.93-1.10 (3H, m), 1.28-2.08 (11H, m), 2.70-2.85 (4H, m), 3.34-3.54 (3H, m), 3.78-4.68 (2H, m), 5.28-5.44 (1H, m), 7.02-7.30 (4H, m), 7.64-7.96 (4H, m), 9.30 (1H, brs), 10.18 and  
30        10.30 (1H, 2 x brs). MS (CI)  $m/e$  460  $[\text{MH}]^+$ . Anal. Found C, 65.32; H, 7.14; N, 13.73.  $\text{C}_{27}\text{H}_{33}\text{N}_5\text{O}_2$ . HCl requires C, 65.38; H, 6.91; N, 14.12%.  $[\alpha]_D^{25} -194.4^\circ$  ( $c=0.50$ , MeOH). Purity A:B > 99.5:0.5.

30        Peak B (0.45g). mp  $159^\circ\text{C}$  (dec.).  $^1\text{H}$  NMR (360MHz,  $\text{D}_6$ -DMSO)  $\delta$  0.93-1.10 (3H, m), 1.28-2.08 (11H, m), 2.70-2.85 (4H, m), 3.34-3.54 (3H, m), 3.78-4.68 (2H, m), 5.28-5.44 (1H, m), 7.02-7.30 (4H, m), 7.64-7.96 (4H, m), 9.39 (1H, brs), 10.20 and 10.35 (1H, 2 x brs). MS (CI)  $m/e$  460  $[\text{MH}]^+$ . Anal. Found C,



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65.14; H, 7.41; N, 13.52.  $C_{27}H_{33}N_5O_2 \cdot HCl \cdot 0.25(Et_2O) \cdot 0.15(H_2O)$  requires C, 65.01; H, 7.17; N, 13.54%.  $[\alpha]_D^{25} +183.5^\circ$  (c=0.50, MeOH). Purity A:B = 0.7:99.3.

5 EXAMPLE 16: N-[3(R,S)-2,3-Dihydro-5-(cis-2,6-  
dimethylmorpholin-4-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-  
3-yl] N'-[3-methylphenyl] urea

a) 1,2-Dihydro-5-(cis-2,6-dimethylmorpholin-4-yl)-1-  
methyl-3H-1,4-benzodiazepin-2-one

10 Prepared as described in Example 4c), from 1-methyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione (10g) and cis-2,6-dimethylmorpholine (6.5ml).  $^1H$  NMR (250MHz,  $CDCl_3$ )  $\delta$  1.10 (3H, d, J=7Hz), 1.24 (3H, d, J=7Hz), 2.40-2.76 (2H, m), 3.20-3.88 (8H, m), 4.29 (1H, d, J=12Hz), 7.19-7.39 (2H, m), 7.47-7.60  
15 (2H, m)..

b) 1,2-Dihydro-5-(cis-2,6-dimethylmorpholin-4-yl)-1-  
methyl-3-oximido-3H-1,4-benzodiazepin-2-one

20 Prepared as described in Example 4), from 1,2-dihydro-5-(cis-2,6-dimethylmorpholin-4-yl)-1-methyl-3H-1,4-benzodiazepin-2-one (4.8g).  $^1H$  NMR (360MHz,  $D_6$ -DMSO)  $\delta$  1.80 (6H, brs), 2.42-2.64 (2H, m), 3.80-4.20 (7H, brm), 7.30 (1H, dd, J=7.0 and 7.0Hz), 7.46-7.60 (3H, m), 10.10-10.42 (1H, 2 x brs). MS (CI) m/e 317  $[MH]^+$ .

25 c) 1,2-Dihydro-5-(cis-2,6-dimethylmorpholin-4-yl)-1-  
methyl-3-(O-ethylaminocarbonyl)oximido-3H-1,4-benzodiazepin-  
2-one

30 Prepared as described in Example 4e), from 1,2-dihydro-5-(cis-2,6-dimethylmorpholin-4-yl)-1-methyl-3-oximido-3H-1,4-benzodiazepin-2-one (1.5g).  $^1H$  NMR (360MHz,  $CDCl_3$ )  $\delta$  1.09-1.26 (9H, m), 2.52-3.40 (2H, brm), 3.22-3.92 (8H, m), 4.36-4.44 and 4.70-4.92 (1H, brm), 6.39 (1H, m), 7.24-7.34 (3H, m), 7.53 (1H, dd, J=7.0 and 7.0Hz). MS (CI) m/e 388  $[MH]^+$ .

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d) N-[3(R,S)-2,3-Dihydro-5-(cis-2,6-dimethylmorpholin-4-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea

To a solution of the product of part c) (1.52g) in methanol (80ml) was added 10% palladium on carbon (400mg, 26% (w/w)). The mixture was hydrogenated at 40 psi for 2h and then the catalyst was filtered off and washed with methanol. The solvent was evaporated *in vacuo* to give the amine (1.06g).

To a stirred solution of the amine (1.06g) in anhydrous tetrahydrofuran (10ml) under an atmosphere of nitrogen, at 0°C, was added *m*-tolyl isocyanate (0.45ml) dropwise. After stirring at 0°C for 5 min the desired compound (1.45g) was collected by filtration and recrystallised from petrol:ethyl acetate (1:1). mp 253-255°C. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.11 (3H, d, J=6.2Hz), 1.17 (3H, d, J=6.2Hz), 2.29 (3H, s), 2.41-2.47 (1H, m), 2.59-2.66 (1H, m), 3.41-3.45 (4H, m), 3.62-3.80 (3H, m), 5.34 (1H, d, J=8.0Hz), 6.69-6.73 (1H, m), 6.83 (1H, d, J=7.1Hz), 7.08-7.16 (3H, m), 7.24-7.35 (3H, m), 7.52-7.57 (2H, m). MS (CI) m/e 436 [MH]<sup>+</sup>.

EXAMPLE 17: N-[3(R,S)-2,3-Dihydro-5-(4-methylpiperidin-1-yl)-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea

a) N-Propylisatoic anhydride

To a stirred solution of isatoic anhydride (100g) and propyl iodide (66ml) in dimethylformamide (600ml) at 0°C, under nitrogen, was added sodium hydride (28g of a 55% dispersion in mineral oil) portionwise. The mixture was allowed to warm to room temperature and stirred for 18h. The solvent was then removed *in vacuo* and the residue partitioned between ethyl acetate (1000ml) and water (500ml). The organic phase was separated, washed with brine (2 x 500ml), dried (MgSO<sub>4</sub>) and evaporated. The residue was triturated with anhydrous

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diethyl ether to give the title compound (57g). <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.06 (3H, t, J=7.5Hz), 1.75-1.86 (2H, m), 4.01-4.05 (2H, m), 7.17 (1H, d, J=8.5Hz), 7.26-7.32 (1H, m), 7.73-7.78 (1H, m), 8.17 (1H, dd, J=7.9 and 1.7Hz). MS (CI) m/e 205 [M]<sup>+</sup>.

5           b) 1-Propyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione

N-Propylisatoic anhydride (56g) and glycine (20.5g) were heated at reflux in glacial acetic acid (375ml), under nitrogen, for 5h. The solution was concentrated *in vacuo* and the residue partitioned between dichloromethane (1500ml) and saturated sodium bicarbonate solution (1000ml). The organic phase was separated, dried (MgSO<sub>4</sub>) and evaporated to afford an orange gum. The gum was cooled to 0°C then triturated with anhydrous diethyl ether to give the bis-lactam (47g) as colourless needles. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 0.84 (3H, t, J=7.3Hz), 1.46-1.66 (2H, m), 3.52-3.64 (1H, m), 3.70-3.85 (2H, m), 4.18-4.28 (1H, m), 7.22-7.36 (3H, m), 7.55 (1H, d of t, J=7.5 and 1.7Hz), 7.90 (1H, dd, J=7.8 and 1.7Hz). MS (CI) m/e 219 [MH]<sup>+</sup>.

15           c) N-[3(R,S)-2,3-Dihydro-5-(4-methylpiperidin-1-yl)-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea

Prepared as described in Example 4, steps c)-f), from 1-propyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione (30g) and 4-methylpiperidine (16.3ml). mp 133-136°C. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 0.79 (3H, t, J=7.4Hz), 0.96 (3H, d, J=6.4Hz), 1.10-1.75 (7H, m), 2.28 (3H, s), 2.76-3.02 (2H, m), 3.55-3.86 (2H, m), 3.91-4.04 (1H, m), 4.23-4.36 (1H, m), 5.35 (1H, d, J=8.2Hz), 6.79-6.84 (2H, m), 7.11-7.14 (2H, m), 7.24-7.40 (4H, m), 7.51-7.59 (2H, m). MS (CI) m/e 448 [MH]<sup>+</sup>.

30           EXAMPLE 18: Chiral separation of N-[3(R,S)-2,3-dihydro-5-(4-methylpiperidin-1-yl)-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea

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N-[3(R,S)-2,3-Dihydro-5-(4-methylpiperidin-1-yl)-2-oxo-1-propyl-H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea (1.74g) was dissolved in 9:1 chloroform:methanol (11ml). 440µl of this solution was injected onto a dinitrobenzoyl leucine column (250 x 20mm i.d., 5µm) per min using 95:5:1 1-chlorobutane:methanol:acetic acid as the mobile phase. Using a flow rate of 20ml/min and u.v. detection at 330nm, the two enantiomers were efficiently separated and isolated as described in Example 5.

Peak A: (0.68g). mp 167-170°C. <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 0.66-1.96 (13H, m), 2.22 (3H, s), 3.00-4.20 (9H, m), 5.30-5.34 (1H, m), 6.74-6.76 (1H, m), 7.08-7.22 (2H, m), 7.22 (1H, s), 7.24-7.40 (1H, m), 7.56-7.62 (1H, m), 7.78-7.98 (3H, m), 9.46-9.58 (1H, m), 10.52-10.64 (1H, m). MS (CI) m/e 448 [MH<sup>+</sup>]. [α]<sub>D</sub><sup>22</sup> -211.3° (c=0.56, MeOH). Purity A:B = >99.5:0.5.

Peak B: (0.71g) mp 164-167°C. <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 0.66-1.96 (13H, m), 2.22 (3H, s), 3.00-4.20 (9H, m), 5.30-5.34 (1H, m), 6.74-6.76 (1H, m), 7.08-7.22 (2H, m), 7.22 (1H, s), 7.24-7.40 (1H, m), 7.56-7.62 (1H, m), 7.78-7.98 (3H, m), 9.46-9.58 (1H, m), 10.52-10.64 (1H, m). MS (CI) m/e 448 [MH<sup>+</sup>]. [α]<sub>D</sub><sup>22</sup> +201.8° (c=0.57, MeOH). Purity A:B = 2:98.

EXAMPLE 19: N-[3(R,S)-2,3-Dihydro-1-methyl-2-oxo-5-(4-trifluoromethylpiperidin-1-yl)-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea

a) 4-Trifluoromethylpiperidine hydrochloride

A solution of 2-chloro-4-trifluoromethylpyridine (11.6g) in glacial acetic acid (70ml), containing 10% palladium on carbon (2.4g, 21% (w/w)) was hydrogenated at 40 psi for 4h. Concentrated hydrochloric acid (20ml) was added and hydrogenation continued for a further 1h. The catalyst was filtered off and the filtrate evaporated *in vacuo* to afford 4-trifluoromethylpyridinium hydrochloride.

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The pyridium hydrochloride was dissolved in ethanol (70ml) and water (5ml), and hydrogenated at 40 psi at 60°C in the presence of 5% rhodium on carbon (4.8g, 41% (w/w)). After 4h the catalyst was filtered off and the filtrate evaporated *in vacuo*.

5 The residue was azeotroped with toluene (30ml) and then triturated with anhydrous diethyl ether. <sup>1</sup>H NMR (250MHz, D<sub>6</sub>-DMSO) δ 1.62-2.01 (4H, m), 2.56-3.00 (3H, m), 3.18-3.39 (2H, m), 9.00-9.60 (2H, 2 x brs). MS (CI) m/e 154 [MH]<sup>+</sup>.

10 b) 1,2-Dihydro-1-methyl-3-(O-ethylaminocarbonyl)oximido-5-(4-trifluoromethylpiperidin-1-yl)-3H-1,4-benzodiazepin-2-one

Prepared as described in Example 4 steps c)-e), from from 1-methyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione (11.1g) and 4-trifluoromethylpiperidine hydrochloride (10.63g).  
15 <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.13 (3H, t, J=7.1Hz), 1.70-2.40 (5H, m), 2.80-3.04 (2H, br m), 3.22-3.30 (2H, m), 3.45 (3H, s), 3.50-4.94 (2H, br m), 6.00-6.10 and 6.35-6.39 (1H, 2 x br s), 7.24-7.38 (3H, m), 7.53 (1H, d of t, J=7.2 and 1.5Hz). MS (CI) m/e 426 [MH]<sup>+</sup>.

20 c) N-[3(R,S)-2,3-Dihydro-1-methyl-2-oxo-5-(4-trifluoromethylpiperidin-1-yl)-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea

The amine was prepared as in Example 4f), from the product of part b). The title compound was then prepared from  
25 the amine and *m*-tolyl isocyanate (490μl) as described in Example 16d). mp 248-250°C. <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 1.30-2.24 (8H, m), 2.40-3.00 (2H, brm), 3.04-4.20 (5H, brm), 5.22-5.40 (1H, brs), 6.75 (1H, d, J=7.2Hz), 7.08-7.17 (2H, m), 7.22 (1H, s), 7.24-7.46 (1H, brm), 7.50-7.60 (1H, m), 7.68-7.72 (1H, m),  
30 7.80-8.00 (2H, m), 9.46 (1H, brs), 10.72 (1H, brs). MS (CI) m/e 474 [MH]<sup>+</sup>.

EXAMPLE 20: Chiral separation of N-[3(R,S)-2,3-dihydro-1-methyl-2-oxo-5-(4-trifluoromethylpiperidin-1-yl)-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea

5 N-[3(R,S)-2,3-Dihydro-1-methyl-2-oxo-5-(4-trifluoromethylpiperidin-1-yl)-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea (1.44g) was dissolved in 9:1 chloroform:methanol (20ml). 1.5ml of this solution was injected onto a dinitrobenzoyl leucine column (250 x 20mm i.d., 5 $\mu$ m) per run using 95:5:1 1-chlorobutane:methanol:acetic acid as the mobile phase. The two enantiomers were efficiently separated and isolated as described in Example 5.

15 Peak A (704mg) mp 185-188°. <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO)  $\delta$  1.30-2.24 (8H, m), 2.40-3.00 (2H, m), 3.04-4.20 (5H, brm), 5.22-5.40 (1H, brs), 6.75 (1H, d, J=7.2Hz), 7.08-7.17 (2H, m), 7.22 (1H, s), 7.24-7.46 (1H, brm), 7.50-7.60 (1H, m), 7.68-7.72 (1H, m), 7.80-8.00 (2H, m), 9.46 (1H, brs), 10.72 (1H, brs). MS (CI) m/e 474 [MH]<sup>+</sup>.  $[\alpha]_D^{22}$  -227.7° (c=0.53, MeOH). Purity A:B = >99.5:0.5.

20 Peak B (0.71g) mp 185-188°C. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>)  $\delta$  1.44-1.62 (1H, m), 1.66-1.98 (3H, m), 2.08-2.22 (1H, m), 2.29 (3H, s), 2.58-3.40 (2H, m), 3.43 (3H, s), 3.58-3.68 (1H, m), 4.01-4.09 (1H, m), 5.30 (1H, d, J=7.9Hz), 6.59 (1H, d, J=7.8Hz), 6.95 (1H, brs), 7.05-7.08 (1H, m), 7.14 (1H, dd, J=7.8 and 7.8Hz), 7.23-7.34 (3H, m), 7.52-7.56 (2H, m). MS (CI) m/e 474 [MH]<sup>+</sup>.  $[\alpha]_D^{22}$  +211° (c=0.52, MeOH). Purity A:B = 2:98.

EXAMPLE 21: N-[3(R,S)-2,3-Dihydro-5-(2,2-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea

30 a) 6,6-Dimethylpiperidin-2-one

To a solution of 2,2-dimethylcyclopentanone (2g) in formic acid (97%, 27ml) was added portionwise hydroxylamine-O-sulphonic acid (3.02g) over a period of 10 min. The mixture was

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heated at reflux for 5h. After cooling, ice was added and the mixture neutralised with sodium hydroxide solution (4M, ~200ml) and then extracted with dichloromethane (4 x 50ml). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent evaporated *in vacuo*. The residue was chromatographed on silica gel using a gradient of 0 to 20% ethyl acetate in dichloromethane, followed by 10% methanol in dichloromethane as eluant, to obtain a colourless solid. This was triturated with hexane to afford the title compound (0.43g). mp 128-131°C.  $^1\text{H}$  NMR (360MHz,  $\text{CDCl}_3$ )  $\delta$  1.25 (6H, s), 1.64-1.68 (2H, m), 1.80-1.88 (2H, m), 2.31 (2H, t,  $J=6.6\text{Hz}$ ), 5.82 (1H, br s). MS (CI)  $m/e$  128  $[\text{MH}]^+$ .

b) 2,2-Dimethylpiperidine

To a solution of lithium aluminium hydride in diethyl ether (66ml of a 1.0M solution) under nitrogen at reflux, was added a suspension of 6,6-dimethylpiperidin-2-one (4.2g) in anhydrous diethyl ether (120ml) portionwise over a period of 15 min. The mixture was heated at reflux under nitrogen for 5h, then cooled to 0°C. Water (2.5ml) was added dropwise, followed by aqueous sodium hydroxide (2.5ml of a 4N solution) and water (7.5ml). The resultant granular solid was removed by filtration, the filtrate dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated. The pale yellow oil was distilled under reduced pressure to afford the title piperidine (2.7g). bp 70°C/60mmHg.  $^1\text{H}$  NMR (360MHz,  $\text{CDCl}_3$ )  $\delta$  1.13 (6H, s), 1.36-1.50 (4H, m), 1.53-1.62 (2H, m), 2.83-2.87 (2H, m). MS (CI)  $m/e$  114  $(\text{MH})^+$ .

c) 1,2-Dihydro-5-(2,2-dimethylpiperidin-1-yl)-1-methyl-3-(O-ethylaminocarbonyl)oximido-3H-1,4-benzodiazepin-2-one

Prepared as described in Example 4 steps c) to e), from 1-methyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione (4.54g), and 2,2-dimethylpiperidine (2.7g).  $^1\text{H}$  NMR (360MHz,  $\text{CDCl}_3$ )  $\delta$  1.20 and 1.25 (3H, 2 x t,  $J=7.3\text{Hz}$ ), 1.43-1.44 (3H, m), 1.55-1.82 (9H, m), 2.93-3.04 (1H, m), 3.19-3.30 (3H, m), 3.43-3.46

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(3H, m), 6.02-6.08 and 6.26-6.32 (1H, m), 7.18-7.34 (2H, m), 7.44-7.52 (2H, m). MS (CI) m/e 386 [MH]<sup>+</sup>.

d) N-[3(R,S)-2,3-Dihydro-5-(2,2-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea

The amine was prepared as in Example 4f), from the product of part c) (2.3g). The title compound was then prepared from the crude amine and *m*-tolyl isocyanate (0.78ml) as described in Example 6b). mp 235°C (dec.). <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.42-1.66 (9H, m), 2.29 (3H, s), 2.80-2.98 (2H, m), 3.42 (3H, s), 5.20 (1H, d, J=7.9Hz), 6.42-6.50 (1H, m), 6.70-6.86 (2H, m), 7.06-7.16 (2H, m), 7.18-7.28 (3H, m), 7.45-7.52 (1H, m), 7.69 (1H, dd, J=7.8 and 1.6Hz). MS (CI) m/e 434 [MH]<sup>+</sup>. Anal. Found: C, 69.13; H, 7.23; N, 16.08. C<sub>25</sub>H<sub>31</sub>N<sub>5</sub>O<sub>2</sub> requires: C, 69.26; H, 7.21; N, 16.15%

EXAMPLE 22: Chiral separation of N-[3(R,S)-2,3-dihydro-5-(2,2-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea

N-[3(R,S)-2,3-dihydro-5-(2,2-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea (1.8g) was dissolved in 9:1 chloroform:methanol (12ml). 400μl of this solution was injected onto a dinitrobenzoyl leucine column (250 x 20mm i.d., 5μm) per run using 90:10:1 1-chlorobutane:methanol:acetic acid as the mobile phase. The two enantiomers were efficiently separated and isolated as described in Example 5.

Peak A (0.8g). mp 150°C (dec.). <sup>1</sup>H NMR (360MHz, d<sub>6</sub>-DMSO) δ 1.17-1.80 (12H, m), 2.23 (3H, s), 2.72-3.82 (5H, m), 5.10-5.28 (1H, m), 6.74 (1H, d, J = 7.0Hz), 7.06-7.36 (4H, m), 7.42-7.58 (1H, m), 7.61-7.98 (3H, m), 9.42 (1H, brs). MS (CI) m/e 434 [M+1]<sup>+</sup>. [α]<sub>D</sub><sup>22</sup> -423.1° (c=0.68, MeOH). Purity A:B = > 99.5:0.5.



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Peak B (0.8g). mp 150°C (dec.). <sup>1</sup>H NMR (360MHz, d<sub>6</sub>-DMSO) δ 1.12-1.83 (12H, m), 2.23 (3H, s), 2.83-3.70 (5H, m), 5.08-5.30 (1H, m), 6.74 (1H, d, J = 6.9Hz), 7.04-7.31 (4H, m), 7.40-7.57 (1H, m), 7.62-7.96 (3H, m), 9.37 (1H, brs). MS (CI) m/e 434 [MH]<sup>+</sup>. [α]<sub>D</sub><sup>22</sup> +420.5° (c=0.67, MeOH). Purity A:B = 1.3:98.7.

EXAMPLE 23: N-[3(R,S)-2,3-Dihydro-1-methyl-2-oxo-5-(cis-2,4,6-trimethylpiperidin-1-yl)-1H-1,4-benzodiazepin-3-yl] N'-(3-methylphenyl) urea

a) 1,2-Dihydro-1-methyl-3-(O-ethylaminocarbonyl)oximido-5-(cis-2,4,6-trimethylpiperidin-1-yl)-3H-1,4-benzodiazepin-2-one

Prepared as described in Example 4 steps c)-e) from 1-methyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione (5g) and cis-2,4,6-trimethylpiperidine (11.7g). <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 0.92-1.50 (14H, m), 1.68-2.23 (3H, m), 3.16-3.30 (2H, m), 3.41-3.47 (3H, m), 3.82-3.88 and 4.07-4.18 (1H, m), 4.54-4.76 (1H, m), 6.13-6.20 and 6.32-6.45 (1H, m), 7.18-7.38 (3H, m), 7.42-7.50 (1H, m). MS (CI) m/e 400 [MH]<sup>+</sup>.

b) N-[3(R,S)-2,3-Dihydro-1-methyl-2-oxo-5-(cis-2,4,6-trimethylpiperidin-1-yl)-1H-1,4-benzodiazepin-3-yl] N'-(3-methylphenyl) urea

The amine was prepared as in Example 4f) from the product of part a). The title compound was then prepared from the crude amine and *m*-tolyl isocyanate (0.8ml) as described in Example 6b) and recrystallised from ethyl acetate: dichloromethane (9:1). mp 223-225°C. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 0.76-1.18 (11H, m), 1.55-1.90 (3H, m), 2.22 (3H, s), 3.29-3.38 (4H, m), 3.56-3.72 (1H, m), 4.97 (1H, d, J = 8.3Hz), 6.71 (1H, d, J = 7.0Hz), 7.05-7.13 (3H, m), 7.16 (1H, s), 7.35 (1H, t, J = 7.0Hz), 7.55 (1H, d, J = 7.9Hz), 7.61-7.65 (2H, m), 8.85 (1H, s). MS (CI) m/e 448 [MH]<sup>+</sup>. Anal. Found: C, 70.00; H, 7.49; N, 15.45. C<sub>26</sub>H<sub>33</sub>N<sub>5</sub>O<sub>2</sub> requires: C, 69.77; H, 7.43; N, 15.65%.

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EXAMPLE 24: Chiral separation of N-[3(R,S)-2,3-dihydro-1-methyl-2-oxo-5-(cis-2,4,6-trimethylpiperidin-1-yl)-1H-1,4-benzodiazepin-3-yl] N'-(3-methylphenyl) urea

N-[3(R,S)-2,3-Dihydro-1-methyl-2-oxo-5-(cis-2,4,6-trimethyl piperidin-1-yl)-1H-1,4-benzodiazepin-3-yl] N'-(3-methylphenyl) urea (1.25g) was dissolved in 9:1 chloroform:methanol (20ml). The enantiomers were separated as described in Example 5.

Peak A (0.59g). mp 170°C (dec.). <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 0.84-1.74 (11H, m), 1.80-2.32 (6H, m), 3.28-3.84 (4H, m), 4.14-4.48 (1H, m), 5.25-5.44 (1H, m), 6.75 (1H, d, J = 7.1Hz), 7.08-7.36 (4H, m), 7.50-7.62 (1H, m), 7.66-7.94 (3H, m), 9.45 (1H, brs), 10.16 (1H, brs). MS (CI) m/e 448 [MH]<sup>+</sup>. Anal. Found: C, 60.42; H, 7.02; N, 13.35. C<sub>26</sub>H<sub>33</sub>N<sub>5</sub>O<sub>2</sub>·HCl·1.75 (H<sub>2</sub>O) requires C, 60.57; H, 7.33; N, 13.58%. [α]<sub>D</sub><sup>22</sup> -138.8° (c=0.64, MeOH). Purity A:B = > 99.5:0.5.

Peak B (0.53g). mp 170°C (dec.). <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 0.84-1.73 (11H, m), 1.80-2.30 (6H, m), 3.32-3.84 (4H, m), 4.16-4.46 (1H, m), 5.24-5.46 (1H, m), 6.75 (1H, d, J = 7.1Hz), 7.07-7.18 (2H, m), 7.20-7.34 (2H, m), 7.50-7.63 (1H, m), 7.66-7.94 (3H, m), 9.45 (1H, brs), 10.14 (1H, brs). MS (CI) m/e 448 [MH]<sup>+</sup>. Anal. Found: C, 62.14; H, 7.10; N, 13.60. C<sub>26</sub>H<sub>33</sub>N<sub>5</sub>O<sub>2</sub>·HCl·H<sub>2</sub>O requires C, 62.20; H, 7.23; N, 13.95%. [α]<sub>D</sub><sup>22</sup> +138.3° (c=0.65, MeOH). Purity A:B = < 0.5:99.5.

EXAMPLE 25: N-[3(R,S)-2,3-Dihydro-5-(3,3-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-(3-methylphenyl) urea

a) 1,2-Dihydro-5-(3,3-dimethylpiperidin-1-yl)-1-methyl-3-oximido-3H-1,4-benzodiazepin-2-one

Prepared as described in Example 4, steps c) and d) from 1-methyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione (16.7g) and 3,3-dimethylpiperidine (10.0g). <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 0.69 (3H, s), 0.82 (3H, s), 1.28-1.45 (3H, m), 1.62-

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1.80 (1H, m), 2.75-3.00 (3H, m), 3.30 (3H, s), 3.50-3.60 (1H, m), 7.25-7.30 (1H, m), 7.40-7.60 (3H, m), 9.95 (1H, br s), 10.20 (1H, br s). TLC (10% MeOH/dichloromethane: silica) R<sub>f</sub> = 0.40.

5        b) N-[3(R,S)-2,3-Dihydro-5-(3,3-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea

10        1,2-Dihydro-5-(3,3-dimethylpiperidin-1-yl)-1-methyl-3-(O-ethylaminocarbonyl)oximido-3H-1,4-benzodiazepin-2-one (11.4g) was prepared as described in Example 4e) from the product of part a). The amine was prepared as in Example 4f) from 1,2-dihydro-5-(3,3-dimethylpiperidin-1-yl)-1-methyl-3-(O-ethylamino-carbonyl)oximido-3H-1,4-benzodiazepin-2-one (11.4g). The title compound was then prepared from the crude amine (8.5g) and *m*-tolyl isocyanate (4ml) as described in  
15        Example 6b). mp 213-215°C. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 0.71 (3H, s), 0.85 (3H, s), 1.30-1.47 (3H, m), 1.64-1.80 (1H, m), 2.22 (3H, s), 2.75-2.82 (1H, m), 2.84-3.00 (2H, m), 3.31 (3H, s), 3.50-3.60 (1H, m), 4.95 (1H, d, J = 8.4Hz), 6.70 (1H, d, J = 6.9Hz), 6.99-7.00 (1H, m), 7.02-7.20 (3H, m), 7.34-7.40 (1H, m), 7.50-7.70  
20        (3H, m), 8.80 (1H, m).

EXAMPLE 26: Chiral separation of N-[3(R,S)-2,3-dihydro-5-(3,3-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea

25        (-)-N-[2,3-dihydro-(3,3-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea was prepared from the racemate analogously to Example 5. <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 0.56 (3H, s), 0.81 (3H, s), 1.40-1.90 (4H, m), 2.24 (3H, s), 3.17 (1H, d, J = 11.8Hz), 3.22-3.60 (2H, m), 3.41  
30        (3H, s), 4.00-4.10 (1H, m), 5.41 (1H, d, J = 6.7Hz), 6.77 (1H, d, J = 8.2Hz), 7.08-7.18 (3H, m), 7.23 (1H, s), 7.34 (1H, d, J = 6.7Hz), 7.58 (1H, t, J = 7.3Hz), 7.79 (1H, d, J = 7.6Hz), 7.78-7.95 (2H, m),

9.26 (1H, s), 10.50 (1H, m). MS (CI) m/e 434 [MH]<sup>+</sup>. Purity A:B 99.5:0.5.  $[\alpha]_D^{25}$  -86.3° (c=0.75, CH<sub>2</sub>Cl<sub>2</sub>).

EXAMPLE 27: N-[3(R,S)-2,3-Dihydro-5-(4,4-dimethylpiperidin-1-yl)-2-oxo-1-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepin-3-yl] N'-(3-methylphenyl) urea

a) Methyl 2-[N-(2-bromoacetyl)-N-(2,2,2-trifluoroethyl)]aminobenzoate

A solution of methyl anthranilate (98.3g) and trifluoroethyl trichloromethanesulphonate (91.5g) in *m*-xylene (200ml) was heated at reflux for 3h under nitrogen. The reaction mixture was allowed to cool overnight, then filtered from a white solid, washing well with diethyl ether. The combined filtrates were evaporated *in vacuo* and the residual oil purified by flash chromatography (silica gel, 10% diethyl ether/hexane) to give methyl 2-[N-(2,2,2-trifluoroethyl)]aminobenzoate, contaminated with trifluoroethyl trichloromethanesulphonate. To a solution of this mixture (35.8g) in dichloromethane (150ml), cooled to 1°C under nitrogen, was added dropwise bromoacetyl bromide (10.1ml), keeping the temperature below +3°C. The reaction mixture was stirred at 0 ± 3°C for 12 min, then 4N NaOH solution (33.4ml) was added dropwise over 18 min. The cooling bath was removed and the reaction mixture was stirred at room temperature for 4h. More bromoacetyl bromide (1.6ml) was added dropwise and the mixture was stirred for a further 6h. After leaving to stand overnight, the organic layer was separated, washed with 10% citric acid (30ml), brine (30ml), saturated potassium carbonate solution (30ml) and brine (30ml), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated *in vacuo* to leave a yellow oil. This was purified by flash chromatography (silica gel, 20-25% EtOAc/petroleum ether) to afford the title compound (27.4g). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.58 (1H, d, J = 11.4Hz), 3.64 (1H, d, J = 11.3Hz), 3.83 (1H, m), 3.90 (3H, s), 4.79 (1H, m), 7.49 (1H, d, J =

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7.8Hz), 7.57 (1H, t of d, J = 7.6 and 1.3Hz), 7.68 (1H, t of d, J = 7.6 and 1.7Hz), 8.09 (1H, dd, J = 7.8 and 1.6Hz). MS (CI+, NH<sub>3</sub>) m/e 373/371 (M+NH<sub>4</sub>)<sup>+</sup>.

5           b)       1,2,3,4-Tetrahydro-1-(2,2,2-trifluoroethyl)-3H-1,4-benzodiazepin-2,5-dione

Ammonia gas was bubbled into a solution of the product of part a) (27.3g) in anhydrous methanol (150ml) for 4h, keeping the temperature at +4 ± 9°C. The reaction mixture was allowed to stand open overnight then nitrogen was bubbled through the solution for 1h. The solvent was removed *in vacuo* and the residue stirred with 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>. The solid was filtered off, washed well with more 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>, and the combined filtrates were purified by flash chromatography (silica gel, 3-5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound (15.2g). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.87 (2H, m), 4.19 (1H, m), 5.03 (1H, m), 6.84 (1H, br s), 7.29 (1H, d, J = 8.3Hz), 7.42 (1H, t of d, J = 7.6 and 0.8Hz), 7.60 (1H, t of d, J = 7.6 and 1.6Hz), 7.93 (1H, dd, J = 7.8 and 1.6Hz). MS (CI+, NH<sub>3</sub>) m/e 259 [MH]<sup>+</sup>.

20           c)       1,2-Dihydro-5-(4,4-dimethylpiperidin-1-yl)-3-(O-ethylaminocarbonyl)oximido-1-(2,2,2-trifluoroethyl)-3H-1,4-benzodiazepin-2-one

Prepared by the procedure of Example 4, steps c)-e) from the product of part b) (18.0g) and 4,4-dimethylpiperidine (3.51g). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.97 and 1.05 (6H, 2 x br s), 1.10 and 1.13 (3H, 2 x t, J = 7.3Hz), 1.16-1.26 (4H, m), 3.25 (2H, m), 3.39-4.11 (5H, m), 5.24-5.42 (1H, m), 6.16 and 6.33 (1H, 2 x br t), 7.31-7.56 (4H, m). MS (CI+, NH<sub>3</sub>) m/e 454 [MH]<sup>+</sup>.

30           d)       N-[3(R,S)-2,3-Dihydro-5-(4,4-dimethylpiperidin-1-yl)-2-oxo-1-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepin-3-yl] N'-(3-methylphenyl) urea

Following the procedure of Example 4f), the product of part c) (450mg) was hydrogenated to give 3-amino-1,2-dihydro-5-(4,4-

dimethylpiperidin-1-yl)-1-(2,2,2-trifluoroethyl)-3H-1,4-benzodiazepin-2-one (313mg). This was dissolved in anhydrous tetrahydrofuran (6ml) under nitrogen and cooled with an ice/water bath before adding *m*-tolyl isocyanate (0.110ml) dropwise. The mixture was stirred for 40 min before removing the cooling bath and stirring for a further hour. The solvent was removed *in vacuo* and the residue triturated with diethyl ether (10ml) to afford the title compound (347mg); mp 236-239°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.96 (6H, s), 1.30-1.50 (4H, m), 2.29 (3H, s), 3.30 (4H, m), 4.08 (1H, m), 5.23 (1H, m), 5.38 (1H, d, J = 8.2Hz), 6.46 (1H, br d, J = 7.9Hz), 6.84-6.88 (2H, m), 7.08-7.17 (2H, m), 7.21 (1H, s), 7.34-7.37 (2H, m), 7.53-7.58 (2H, m). MS (CI<sup>+</sup>, NH<sub>3</sub>) m/e 502 [MH]<sup>+</sup>. Anal. Found: C, 61.21; H, 5.88; N, 13.19% C<sub>26</sub>H<sub>30</sub>F<sub>3</sub>N<sub>5</sub>O<sub>2</sub>·0.6H<sub>2</sub>O·0.1 C<sub>4</sub>H<sub>8</sub>O requires: C, 61.03; H, 6.21; N, 13.48%.

EXAMPLE 28: Chiral separation of N-[3(R,S)-2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-2-oxo-1-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea

A solution of N-[3(R,S)-2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-2-oxo-1-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea (330mg) in 50% CHCl<sub>3</sub>/EtOH (5ml) was injected in 0.5ml volumes onto a dinitrobenzoyl leucine column (250 x 20.4mm i.d., 5µm), eluting with 50% ethanol/hexane at 20ml/min. The fractions containing each enantiomer were separately evaporated *in vacuo*, the residues were redissolved in filtered dichloromethane (10ml) and ethereal hydrogen chloride (2ml) was added. The solvents were then removed *in vacuo* and the residues triturated with diethyl ether (5ml) to give:

Peak A. HCl salt (134mg); mp 153-158°C; <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) at 353K: δ 0.98 (6H, s), 1.26-1.51 (4H, m), 2.23 (3H, s), 3.41-3.63 (4H, br m), 4.73 (1H, m), 5.15 (1H, m), 5.35 (1H, m),

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6.75 (1H, d, J = 7.1Hz), 7.06-7.20 (4H, m), 7.59 (1H, m), 7.78-7.85 (3H, m), 9.16 (1H, br s). MS (CI<sup>+</sup>, NH<sub>3</sub>) m/e 502 [MH]<sup>+</sup>. [α]<sub>D</sub><sup>25</sup> = -195.5° (c=0.2, MeOH). Purity A:B = > 99.5:0.5. Anal. Found: C, 55.83; H, 6.04; N, 11.93%. C<sub>26</sub>H<sub>30</sub>F<sub>3</sub>N<sub>5</sub>O<sub>2</sub>·HCl.1.42 H<sub>2</sub>O 0.06 C<sub>4</sub>H<sub>10</sub>O. requires C, 55.48; H, 6.11; N, 12.33%.

Peak B. HCl salt (128mg); mp 145-151°C; <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) at 353K same as for Peak A. MS (CI<sup>+</sup>, NH<sub>3</sub>) m/e 502 [MH]<sup>+</sup>. [α]<sub>D</sub><sup>25</sup> = +204° (c=0.2, MeOH). ee = 99%. Anal. Found: C, 56.67; H, 5.86; N, 12.29%. C<sub>26</sub>H<sub>30</sub>F<sub>3</sub>N<sub>5</sub>O<sub>2</sub>·HCl.0.8 H<sub>2</sub>O: requires C, 56.53; H, 5.95; N, 12.68%.

EXAMPLE 29: N-[3(R,S)-2,3-Dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-ethyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea

a) 1,2-Dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-ethyl-3-(O-ethylaminocarbonyl)oximido-3H-1,4-benzodiazepin-2-one

Prepared as described in Example 4, steps c) to e) from 1-ethyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione (18g) and 4,4-dimethylpiperidine (10g). <sup>1</sup>H NMR (360MHz, d<sub>6</sub>-DMSO) δ 0.9-1.20 (16H, br m), 2.94-3.03 (2H, m), 3.1-3.96 (5H, br m), 4.26 (1H, m), 7.2-7.7 (5H, m).

b) N-[3(R,S)-2,3-Dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-ethyl-2-oxo-5-(4,4-dimethylpiperidin-1-yl)-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea

The amine was prepared as in Example 4f) from the product of part a) (5.2g). The title compound was then prepared from the amine and *m*-tolyl isocyanate (1.6ml) as described in Example 16d) and recrystallised from petroleum ether.

EXAMPLE 30: Chiral separation of N-[3(R,S)-2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-ethyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea

N-[3(R,S)-2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-ethyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl] urea (2.4g) was dissolved in 9:1 chloroform:methanol (20ml). 1ml of this solution was injected onto a dinitrobenzoyl leucine column (250 x 20mm i.d., 5µM) per run using 96:3:1 chlorobutane:methanol:acetic acid as the mobile phase. Using a flow rate of 20ml/min and u.v. detection at 330nm, the two enantiomers were efficiently separated. The fractions containing enantiomer A were combined and evaporated under reduced pressure. The residue was partitioned between ethyl acetate (50ml) and potassium carbonate solution. The organic phases were separated, dried (MgSO<sub>4</sub>), filtered and evaporated under reduced pressure to give a foam.

Peak A was purified using the Gilson Prep HPLC using 3:2 acetonitrile/water (containing 0.1% TFA) as mobile phase. The solution containing the desired product was evaporated under reduced pressure to remove the acetonitrile. The aqueous solution was basified with sodium carbonate and extracted with ethyl acetate (3 x 100ml). The ethyl acetate extracts were combined, dried (MgSO<sub>4</sub>), filtered and evaporated to give a foam (0.45g). The foam was recrystallised from diethyl ether (0.28g). mp 211-213°C. Found: C, 69.82; H, 7.24; N, 15.60. C<sub>26</sub>H<sub>33</sub>N<sub>5</sub>O<sub>2</sub> requires C, 69.77; H, 7.43; N, 15.65. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 0.95 (6H, s), 1.09 (3H, t), 1.31 (2H, m), 1.47 (2H, m), 2.28 (3H, s), 3.2 (4H, br m), 3.68 (1H, m), 4.33 (1H, m), 5.30 (1H, d), 6.74 (1H, d), 6.80 (1H, d), 7.07-7.37 (6H, m), 7.52 (2H, m).

EXAMPLE 31: N-[3(R,S)-5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl] urea

Method A

a) 5-(3-Azabicyclo[3.2.2]nonan-3-yl)-1,3-dihydro-2H-1-methyl-3-oximido-1,4-benzodiazepin-2-one



Prepared analogously to Example 4, steps c) and d) from 1-methyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione (10.0g) and 3-azabicyclo[3.2.2]nonane (6.89g). mp 220-222°C. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.30-2.30 (10H, m), 3.32-3.40 (1H, m), 3.45 (3H, s), 3.47-3.54 (1H, m), 3.74-3.80 (1H, m), 4.66-4.73 (1H, m), 7.20-7.35 (3H, m), 7.49 (1H, ddd, J<sub>1</sub> = J<sub>2</sub> = 7Hz, J<sub>3</sub> = 1Hz). Found: C, 66.31; H, 6.93; N, 17.07. C<sub>18</sub>H<sub>22</sub>N<sub>4</sub>O<sub>2</sub> requires C, 66.24; H, 6.79; N, 17.17%.

b) 3(R,S)-Amino-5-(3-azabicyclo[3.2.2]nonan-3-yl)-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one

The foregoing oxime (6.68g) was hydrogenated over 5% rhodium on carbon (6.7g) in methanol (670ml) at 40 psi and 60°C for 6.5 hours. The mixture was filtered then evaporated to give the crude amine which was used immediately in the next step.

c) N-[3(R,S)-5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-(3-methylphenyl) urea

m-Tolyl isocyanate (3.17ml) was added to an ice cold solution of the foregoing amine (6.4g) in anhydrous tetrahydrofuran (70ml) then left standing at 4°C for 16 hours. The solution was evaporated and the residue partitioned between potassium carbonate solution (100ml) and dichloromethane (200ml). The organic layer was separated and the aqueous re-extracted with dichloromethane (5 x 100ml). The combined organics were dried (sodium sulphate) then evaporated and the crude product crystallised from dichloromethane to afford the title compound (1.55g). mp > 242°C (dec.). <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.54-2.04 (10H, m), 2.29 (3H, s), 3.26-3.40 (2H, m), 3.42 (3H, s), 3.52-3.60 (2H, m), 5.28 (1H, d, J = 8Hz), 6.44 (1H, d, J = 8Hz), 6.80-6.84 (2H, m), 7.07-7.16 (2H, m), 7.22-7.33 (3H, m), 7.47-7.55 (2H, m). Found: C, 63.39; H, 6.65; N, 14.15. C<sub>26</sub>H<sub>31</sub>N<sub>5</sub>O<sub>2</sub> · 2H<sub>2</sub>O · 0.15CH<sub>2</sub>Cl<sub>2</sub> requires C, 63.54; H, 7.20; N, 14.17%.

Method B

a) 5-(3-Azabicyclo[3.2.2]nonan-3-yl)-1,3-dihydro-2H-1-methyl-3-(O-(ethylaminocarbonyl)oximido)-1,4-benzodiazepin-2-one

5            5-(3-Azabicyclo[3.2.2]nonan-3-yl)-1,3-dihydro-2H-1-methyl-3-oximido-1,4-benzodiazepin-2-one (5.17g) and ethylisocyanate (1.9ml) were heated at 60°C in anhydrous tetrahydrofuran (200ml) for 18 hours. The solvent was evaporated and the residue was purified by column chromatography on silica using  
10    dichloromethane - 1% methanol/dichloromethane to afford a cream foam (5.53g, 90%, mixture of E/Z isomers). mp 168°C. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.10 and 1.12 (3H, each t, J=7Hz), 1.24-1.96 (9H, m), 2.16-2.28 (1H, m), 3.12-3.36 (3H, m). 3.38-3.52 (1H, m) overlapped with 3.44 and 3.45 (3H, each s), 3.58-3.70  
15    (1H, m), 4.56-4.78 (1H, m), 6.13-6.22 and 6.36-6.44 (1H, each m), 7.18-7.52 (4H, m).

b) 3(R,S)-Amino-5-(3-azabicyclo[3.2.2]nonan-3-yl)-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one

20            5-(3-Azabicyclo[3.2.2]nonan-3-yl)-1,3-dihydro-2H-1-methyl-3-(O-(ethylaminocarbonyl)oximido)-1,4-benzodiazepin-2-one (5.4g) was hydrogenated at 40 psi in methanol (500ml) over 10% palladium on carbon (1.8g) for 3 hours at room temperature. The mixture was filtered then evaporated to dryness to afford the title amine (4.45g)

25            c) N-[3(R,S)-5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-(3-methylphenyl) urea

30            The foregoing amine (4.45g) in anhydrous tetrahydrofuran (15ml) was treated with m-tolylisocyanate (1.9ml). After standing for 10 minutes the precipitate was collected to afford the title compound free base (4.90g) which had the same chromatographic and spectroscopic characteristics as the product obtained using Method A.

EXAMPLE 32: N-[3(R,S)-2,3-Dihydro-5-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl] urea

a) 1,3-Dihydro-5-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2H-1-propyl-1,4-benzodiazepin-2-one

Prepared analogously to Example 4c) from 1-propyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione (5.0g) and (1S,4S)-2-methyl-2,5-diazabicyclo[2.2.1]heptane dihydrobromide (17.3g), *J. Org. Chem.* 1990, **55**, 1684-1687).

b) 1,3-Dihydro-5-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2H-3-oximido-1-propyl-1,4-benzodiazepin-2-one

Potassium t-butoxide (3.6g) was added in portions to a stirred, cooled (-20°C) suspension of 1,3-dihydro-5-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2H-1-propyl-1,4-benzodiazepin-2-one (2.0g) in anhydrous toluene (250ml) under a nitrogen atmosphere. After stirring at -20°C for 30 minutes isopentyl nitrite (1.9ml) was added and the reaction mixture was stirred at -20°C for 1 hour then at room temperature for 3 days. The mixture was re-cooled to -20°C and further potassium t-butoxide (1.8g) and isopentyl nitrite (1ml) were added. The mixture was stirred at -20°C for 1 hour then at room temperature for 1 day. The reaction mixture was treated with solid carbon dioxide then evaporated to dryness. The residue was purified by column chromatography on alumina using dichloromethane - 10% methanol/dichloromethane (containing 1% ammonia) to afford the oxime (0.60g). MS, m/z = 341 for M<sup>+</sup>.

c) 3(R,S)-Amino-1,3-dihydro-5-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2H-1-propyl-1,4-benzodiazepin-2-one

Trifluoroacetic acid (1.36ml) and activated zinc powder (Fieser and Fieser, 1967, Volume 1, 1276, 1.14g) were added to a

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stirred solution of the foregoing oxime (0.6g) in glacial acetic acid (70ml) at 40°C then the mixture was stirred at this temperature for 6 hours. The reaction mixture was cooled, filtered then evaporated to dryness to give the crude amine trifluoroacetate.

5           d)           N-[3(R,S)-2,3-Dihydro-5-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl] urea

10           Triethylamine (0.3ml) was added to a stirred suspension of the foregoing amine trifluoroacetate in anhydrous tetrahydrofuran (30ml). The reaction mixture was then treated with m-tolylisocyanate (0.3ml) and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was evaporated to dryness then the residue was partitioned between ethyl acetate (50ml) and 1M citric acid (50ml). The  
15           organic layer was extracted with a further portion of 1M citric acid (50ml) and the combined aqueous was washed with ethyl acetate (3 x 50ml) then basified to pH > 9 with sodium bicarbonate and extracted with ethyl acetate (3 x 50ml). The combined organics were dried (sodium sulphate) then evaporated  
20           to dryness to give a solid which was purified by column chromatography on silica using dichloromethane - 20% methanol/dichloromethane (containing 1% ammonia). The resulting solid was recrystallised from ethanol/water to afford the title compound (25mg) as a 1:1 mixture of diastereomers. mp  
25           126-128°C. MS, CI<sup>+</sup>, m/z = 461 for (M+H)<sup>+</sup>. Found: C, 65.07; H, 7.08; N, 16.94. C<sub>26</sub>H<sub>32</sub>N<sub>6</sub>O<sub>2</sub> · 1.25H<sub>2</sub>O requires C, 64.64; H, 7.20; N, 17.39%.

30           EXAMPLE 33: (-)-N-[5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl] urea Hydrochloride

The racemic compound (Example 31, 1.5g) was separated into its enantiomers using semi-preparative chiral HPLC on a

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Pirkle dinitrobenzoylleucine column (5 $\mu$ ) [(250 x 21.4)mm] eluting with 3% methanol in 1-chlorobutane (including 1% acetic acid). Flow rate 20ml/minute, U.V. detection at 290nm. Analysis was performed on an analytical Pirkle dinitrobenzoylleucine column (5 $\mu$ ) [(250 x 4.6)mm] eluting with 5% methanol in 1-chlorobutane (including 1% acetic acid). Flow rate 1ml/minute, U.V. detection at 250nm.

The free base was liberated and obtained as a colourless solid (680mg). The hydrochloride salt had mp 188-190°C (dec.) (ethyl acetate/acetone (10:1). R<sub>f</sub> 0.55 in dichloromethane/methanol (9:1) on silica plates. MS, CI<sup>+</sup>, m/z = 446 for (M+H)<sup>+</sup>.  $[\alpha]^{23^\circ}_D = -216^\circ$  (c=0.2, methanol). Found: C, 63.75; H, 6.99; N, 13.98. C<sub>26</sub>H<sub>31</sub>N<sub>5</sub>O<sub>2</sub>.HCl.0.5H<sub>2</sub>O requires C, 63.60; H, 6.77; N, 14.26%. HPLC: (Pirkle dinitrobenzoylleucine column, 5% methanol in 1-chlorobutane (including 1% acetic acid)): > 99% ee (R<sub>t</sub> = 5.6 minutes). HPLC: (Spherisorb 5 $\mu$ m Phenyl column [(250 x 4.6)mm], 50% acetonitrile/50% of 0.2% triethylamine in water and 50mM potassium phosphate, pH = 3): > 99% chemically pure.

EXAMPLE 34: (+)-N-[5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl] urea Hydrochloride

The title compound was obtained (660mg) using the procedure described in Example 33. The hydrochloride salt had mp 189-191°C (dec.) (ethyl acetate/acetone (10:1)). R<sub>f</sub> 0.55 in dichloromethane/methanol (9:1) on silica plates. MS, CI<sup>+</sup>, m/z = 446 for (M+H)<sup>+</sup>.  $[\alpha]^{23^\circ}_D = +222^\circ$  (c=0.2, methanol). Found: C, 63.59; H, 7.05; N, 13.86. C<sub>26</sub>H<sub>31</sub>N<sub>5</sub>O<sub>2</sub>.HCl.0.5H<sub>2</sub>O requires C, 63.60; H, 6.77; N, 14.26%. HPLC: (Pirkle dinitrobenzoylleucine column, 5% methanol in 1-chlorobutane (including 1% acetic acid)): 99% ee (R<sub>t</sub> = 8.24 minutes). HPLC: (Spherisorb 5 $\mu$ m Phenyl column [(250 x 4.6)mm], 50% acetonitrile/50% of 0.2%

triethylamine in water and 50mM potassium phosphate, pH = 3):  
> 99% chemically pure.

5 EXAMPLE 35: N-[3(R,S)-5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-  
dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-  
fluorophenyl] urea

10 The title compound was obtained (450mg) from  
3-fluorophenyl isocyanate and 3(R,S)-amino-5-(3-azabicyclo  
[3.2.2]nonan-3-yl)-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-  
one as described in Example 31, Method A. mp 196-197°C  
15 (dichloromethane/diethyl ether). MS, CI<sup>+</sup>, m/z = 450 for (M+H)<sup>+</sup>.  
<sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.54-1.90 (8H, m), 1.95-2.02 (2H,  
m), 3.26-3.40 (2H, m), 3.43 (3H, s), 3.52-3.62 (2H, m), 5.28 (1H,  
d, J=8Hz), 6.62-6.67 (2H, m), 6.98 (1H, dd, J<sub>1</sub>=1Hz, J<sub>2</sub>=8Hz),  
7.10-7.55 (7H, m). Found: C, 67.23; H, 6.12; N, 15.46.  
C<sub>25</sub>H<sub>28</sub>FN<sub>5</sub>O<sub>2</sub> requires C, 66.80; H, 6.28; N, 15.58%.

20 EXAMPLE 36: (-)-N-[5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-  
dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-  
fluorophenyl] urea Hydrochloride

25 The racemic compound (Example 35, 320mg) was  
separated into its enantiomers using semi-preparative HPLC on  
a Pirkle dinitrobenzoylleucine column (5μ) [(250 x 21.4)mm]  
eluting with 5% methanol in 1-chlorobutane (including 1% acetic  
acid).

30 The free base was liberated and obtained as a colourless  
solid (140mg). The hydrochloride salt had mp 208-210°C  
(acetone/ethyl acetate (1:1)). [α]<sub>D</sub><sup>24°C</sup> = -235° (c=0.2, methanol).  
<sup>1</sup>H NMR (360MHz, D<sub>2</sub>O) δ 1.24-1.98 (9H, m), 2.28-2.36 (1H, m),  
3.50 (3H, s), 3.61 (1H, d, J=15Hz), 3.70 (1H, d, J=15Hz),  
3.76-3.84 (1H, m), 3.96-4.04 (1H, m), 5.58 (1H, s), 6.88 (1H, ddd,  
J<sub>1</sub>=1Hz, J<sub>2</sub>=J<sub>3</sub>=8Hz), 7.07 (1H, d, J=8Hz), 7.21 (1H, ddd,  
J<sub>1</sub>=J<sub>2</sub>=1Hz, J<sub>3</sub>=8Hz), 7.33 (1H, ddd, J<sub>1</sub>=J<sub>2</sub>=J<sub>3</sub>=8Hz), 7.58 (1H, dd,

$J_1=J_2=8\text{Hz}$ ), 7.65 (1H, d,  $J=8\text{Hz}$ ), 7.75 (1H, d,  $J=8\text{Hz}$ ), 7.86 (1H, dd,  $J_1=J_2=8\text{Hz}$ ). Found: C, 60.84; H, 6.15; N, 13.32.  $\text{C}_{25}\text{H}_{28}\text{FN}_5\text{O}_2\cdot\text{HCl}\cdot 0.5\text{H}_2\text{O}\cdot 0.5\text{CH}_3\text{COCH}_3$  requires C, 60.74; H, 6.35; N, 13.36%

5

EXAMPLE 37: (+)-N-[5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-fluorophenyl] urea Hydrochloride

The title compound was obtained (115mg) using the procedure described in Example 36. The hydrochloride salt had mp 207-209°C (acetone/ethyl acetate (1:1)).  $[\alpha]^{24^\circ\text{C}}_{\text{D}} = +240^\circ$  (c=0.2, methanol). Found: C, 60.87; H, 6.23; N, 13.44.  $\text{C}_{25}\text{H}_{28}\text{FN}_5\text{O}_2\cdot\text{HCl}\cdot 0.5\text{H}_2\text{O}\cdot 0.5\text{CH}_3\text{COCH}_3$  requires C, 60.74; H, 6.35; N, 13.36%.

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EXAMPLE 38: N-[3(R,S)-5-(3-Azabicyclo[3.2.1]octan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl] urea

a) 5-(3-Azabicyclo[3.2.1]octan-3-yl)-1,3-dihydro-2H-1-methyl-3-oximido-1,4-benzodiazepin-2-one

The title compound was obtained from 1-methyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione and 3-azabicyclo[3.2.1]octane (J. Pharm. Sci. 1968, 57, 1785-1787) as described in Example 4, steps c) and d). mp 249-252°C (ethyl acetate/diethyl ether). MS,  $\text{CI}^+$ ,  $m/z = 313$  for  $(\text{M}+\text{H})^+$ . Found: C, 62.28; H, 6.41; N, 16.54.  $\text{C}_{17}\text{H}_{20}\text{N}_4\text{O}_2\cdot\text{H}_2\text{O}$  requires C, 61.80; H, 6.71; N, 16.95%.

25

b) N-[3(R,S)-5-(3-Azabicyclo[3.2.1]octan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl] urea

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The title compound was obtained (1.75g) from the foregoing oxime as described in Example 31, Method A. mp 237-239°C. MS,  $\text{CI}^+$ ,  $m/z = 432$  for  $(\text{M}+\text{H})^+$ .  $^1\text{H}$  NMR (360MHz,

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CDCl<sub>3</sub>) δ 1.46-1.49 (6H, m), 1.90-2.24 (2H, m), 2.28 (3H, s), 2.74-2.82 (1H, m), 3.06-3.12 (1H, m), 3.40-3.50 (2H, m), 3.42 (3H, s), 5.35 (1H, d, J=8Hz), 6.66-6.78 (1H, m), 6.81 (1H, d, J=8Hz), 7.06-7.58 (8H, m). Found: C, 69.38; H, 6.79; N, 15.92.

5 C<sub>25</sub>H<sub>29</sub>N<sub>5</sub>O<sub>2</sub> requires C, 69.58; H, 6.77; N, 16.23%.

EXAMPLE 39: (-)-N-[5-(3-Azabicyclo[3.2.1]octan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl] urea Hydrochloride

10 The title compound free base was obtained (580mg) from the racemate (Example 38, 1.4g) using the procedure described in Example 36. The hydrochloride salt had mp 218-220°C (acetone/ethyl acetate (1:1)).  $[\alpha]^{23^\circ}_D = -215.5^\circ$  (c=0.2, methanol). MS, CI<sup>+</sup>, m/z = 432 for (M+H)<sup>+</sup>. Found: C, 62.90; H, 6.46; N, 14.59. C<sub>25</sub>H<sub>29</sub>N<sub>5</sub>O<sub>2</sub>·HCl·0.5H<sub>2</sub>O requires C, 62.95; H, 6.55; N, 14.68%.

EXAMPLE 40: (+)-N-[5-(3-Azabicyclo[3.2.1]octan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl] urea Hydrochloride

20 The title compound free base was obtained (610mg) from the racemate (Example 38, 1.4g) using the procedure described in Example 36. The hydrochloride salt had mp 190°C (dec.) MS, CI<sup>+</sup>, m/z = 432 for (M+H)<sup>+</sup>.  $[\alpha]^{23^\circ}_D = +182^\circ$  (c=0.2, methanol). Found: C, 62.77; H, 6.66; N, 14.07. C<sub>25</sub>H<sub>29</sub>N<sub>5</sub>O<sub>2</sub>·HCl·0.6H<sub>2</sub>O·0.1CH<sub>3</sub>CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> requires C, 62.56; H, 6.61; N, 14.36%.

EXAMPLE 41: (-)-N-[5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[5-indanyl] urea

30 a) α-amino-N-(5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl) benzenepropanamide



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To a stirred solution of 3(*R,S*)-amino-5-(3-azabicyclo [3.2.2]nonan-3-yl)-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one (2.22g) in anhydrous dimethylformamide (25ml) were added BOC-D-phenylalanine (2.07g), 1-hydroxybenzotriazole (1.02g), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (1.49g) and triethylamine (5ml). After stirring at room temperature for 30 minutes, the reaction mixture was left standing at 4°C for 16 hours. The solvent was evaporated and the residue partitioned between ethyl acetate and 10% potassium carbonate solution. The organic layer was dried (sodium sulphate), evaporated to dryness, and the resulting oil purified by column chromatography on silica using dichloromethane-methanol/dichloromethane (1:99). The product obtained (2.7g) was treated at 4°C with ethyl acetate (15ml), saturated with hydrogen chloride gas and stirred at room temperature for 40 minutes. The solution was cooled down to 4°C and basified with saturated potassium hydrogen carbonate solution, the organic layer was separated and the aqueous re-extracted with ethyl acetate (30ml). The combined organics were dried (sodium sulphate) and evaporated to dryness. The resulting oil was purified by column chromatography on silica using dichloromethane to ammonia/methanol/ dichloromethane (0.2: 2:98) (gradient elution) to afford diastereomer A (0.38g) HPLC (Spherisorb ODS2 column, 70% acetonitrile/30% of 0.2% triethylamine in water, pH to 3 with orthophosphoric acid):  $R_t$  6.8 minutes, and diastereomer B (0.51g, 23%),  $R_f$  0.37 in methanol/dichloromethane (1:9) on silica plates, HPLC (same conditions as in diastereomer A):  $R_t$  8.4 minutes.

b) (-)-3-Amino-5-(3-Azabicyclo[3.2.2]nonan-3-yl)-1,3-dihydro-1-methyl-2H-benzodiazepin-2-one Trifluoroacetate

Phenyl isothiocyanate (120µl) was added to a stirred solution of the foregoing diastereomeric amide A (380mg) in anhydrous dichloromethane (10ml) then heated at 40°C (oil bath

temperature) for 3 hours. The reaction mixture was evaporated and the residue purified by column chromatography on silica using dichloromethane - methanol/dichloromethane (5:95), to afford the thiourea (440mg). Anhydrous trifluoroacetic acid (16.8ml) was added to the solid thiourea (430mg) and the solution stirred at room temperature for 50 minutes. The mixture was evaporated to dryness and the yellow oil azeotroped with toluene. The residue was partitioned between water and diethyl ether, then the aqueous was freeze dried and azeotroped with toluene to afford the homochiral amine trifluoroacetate (218mg). Rf 0.30 in methanol/dichloromethane (1:9) on silica plates,  $[\alpha]^{23^\circ}_D = -20.5^\circ$  (c=0.2, methanol).

c) (-)-N-[5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[5-indanyll urea

A stirred, cooled (0°C) solution of 5-aminoindan (81mg) in anhydrous tetrahydrofuran (15ml) was treated with triphosgene (60.4mg) and triethylamine (250µl). After stirring at 0°C for 15 minutes a solution of (-)-3-amino-5-(3-azabicyclo[3.2.2]nonan-3-yl)-1,3-dihydro-1-methyl-2H-benzodiazepin-2-one trifluoroacetate (218mg) in anhydrous tetrahydrofuran (15ml) was added. After stirring at 0°C for 10 minutes the reaction mixture was left standing at 4°C for 2 days. The reaction mixture was evaporated to dryness and the residue partitioned between saturated potassium carbonate solution and ethyl acetate. The organic layer was dried (sodium sulphate) then evaporated and the residue purified by column chromatography on silica using dichloromethane 2% methanol in dichloromethane (gradient elution). The title compound was obtained as a colourless solid (145mg, 60%). mp 256°C.  $[\alpha]^{22^\circ}_D = -124^\circ$  (c=0.1, methanol).  $^1\text{H}$  NMR (360MHz, DMSO- $d_6$ )  $\delta$  1.5-1.66 (6H, m), 1.76-1.87 (2H, m), 1.9-2.04 (4H, m), 2.76 (4H, dd,  $J_1=J_2=6.5\text{Hz}$ ), 3.23-3.36 (2H, m), 3.32 (3H, s), 3.6-3.7 (2H, m), 4.96 (1H, d,  $J=7\text{Hz}$ ), 6.79 (1H, d,  $J=7\text{Hz}$ ), 7.0-7.64 (7H, m), 8.78

(1H, s). Found: C, 71.59; H, 6.82; N, 14.73.  $C_{28}H_{33}N_5O_2$  requires C, 71.31; H, 7.05; N, 14.85%.

5 EXAMPLE 42: N-[3(R,S)-5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-trifluoromethyl-phenyl] urea

The title compound was obtained (690mg) from 3(R,S)-amino-5-(3-azabicyclo[3.2.2]nonan-3-yl)-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one and 3-trifluoromethylphenyl isocyanate as described in Example 31, Method A. mp 152-154°C (dichloromethane/diethyl ether (2:1)). MS,  $CI^+$ ,  $m/z$  = 500 for  $(M+H)^+$ . Found: C, 60.58; H, 5.96; N, 12.91.  $C_{26}H_{28}F_3N_5O_2 \cdot H_2O$  requires C, 60.34; H, 5.84; N, 13.50%.

15 EXAMPLE 43: N-[3(R,S)-2,3-Dihydro-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl] urea

Prepared analogously to Example 32 from 1-propyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione and 8-methyl-3,8-diazabicyclo[3.2.1] octane (J. Med. Chem. 1974, 17, 481-487). mp 247-250°C. MS,  $CI^+$ ,  $m/z$  = 474  $(M+H)^+$ .  $^1H$  NMR (360MHz,  $DMSO-d_6$ )  $\delta$  0.70 (3H, t,  $J$  = 7Hz), 1.24 (1H, m), 1.39 (1H, m), 1.57 (1H, m), 1.79 (1H, m), 1.92 (1H, m), 2.15 (3H, s), 2.21 (3H, s), 2.62 (1H, m), 3.0 (4H, m), 3.62 (1H, m), 4.42 (1H, m), 4.93 (1H, d,  $J$  = 8Hz), 6.71 (1H, d,  $J$  = 7Hz), 6.98 (1H, d,  $J$  = 8Hz), 7.06 (3H, m), 7.59 (4H, m), 9.80 (1H, s). Found: C, 67.99; H, 6.95; N, 17.54.  $C_{27}H_{34}N_6O_2$  requires C, 67.68; H, 7.26; N, 17.19%.

30 EXAMPLE 44: N-(3(R,S)-5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl)-N'-[3-fluoro-4-methylphenyl] urea

Prepared as described in Example 31, Method B. mp 254-255°C. Found: C, 65.87; H, 6.36; N, 14.54.  $C_{26}H_{30}FN_5O_2 \cdot 0.5H_2O$  requires C, 66.08; H, 6.61; N, 14.82%.

5 EXAMPLE 45: (-)-N-[5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-fluoro-4-methylphenyl] urea Hydrochloride

10 The racemic compound (Example 44, 1.5g) was separated into its enantiomers using semi-preparative HPLC on a Pirkle dinitrobenzoylleucine column (5 $\mu$ ) [(250 x 21.4)mm] eluting with 3% methanol in 1-chlorobutane (including 1% acetic acid). 20ml/minute,  $\lambda$  = 305nm.

15 The fractions from peak A were evaporated to dryness and the free base liberated and obtained as a colourless foam (660mg). The hydrochloride salt had mp 235-236°C (acetone/ethyl acetate).  $[\alpha]^{23^\circ}_D = -242^\circ$  (c=0.2, methanol).  $^1H$  NMR (360MHz,  $DMSO-d_6$ )  $\delta$  1.50-1.80 (10H, m), 2.12 (3H, d, J = 2Hz), 3.10-3.38 (1H, m), 3.41 (3H, s), 3.44-3.58 (2H, m), 3.70-4.00 (1H, m), 5.28-5.36 (1H, broad d), 6.90-7.86 (8H, m), 9.46 (1H, broad s). Found: C, 61.65; H, 6.20; N, 13.49.  $C_{26}H_{30}FN_5O_2 \cdot HCl \cdot 0.5H_2O$  requires C, 61.35; H, 6.33; N, 13.75%.

25 EXAMPLE 46: (+)-N-[5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-fluoro-4-methylphenyl] urea Hydrochloride

The title compound was obtained using the procedure described in Example 45. The fractions from peak B were evaporated to dryness and the free base liberated and obtained as a colourless foam (560mg). The hydrochloride salt had mp 232-234°C (acetone/ethyl acetate).  $[\alpha]^{23^\circ}_D = +275^\circ$  (c=0.2, methanol). Found: C, 61.54; H, 6.30; N, 13.23.  $C_{26}H_{30}FN_5O_2 \cdot HCl \cdot 0.5H_2O \cdot 0.1CH_3CO_2CH_2CH_3$  requires C, 61.23; H, 6.38; N, 15.52%.

EXAMPLE 47: N-[3(R,S)-5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-iodophenyl] urea

5           The title compound was obtained from 3(R,S)-amino-5-(3-azabicyclo[3.2.2]nonan-3-yl)-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one (Example 31, Method B) and m-iodoaniline as described in Example 41. mp > 176°C (chloroform). MS, CI<sup>+</sup>, m/z = 558 for (M+H)<sup>+</sup>. Found: C, 52.02; H, 5.00; N, 11.86.  
10       C<sub>25</sub>H<sub>28</sub>IN<sub>5</sub>O<sub>2</sub>·H<sub>2</sub>O requires C, 52.18; H, 5.25; N, 12.17%.

EXAMPLE 48: (-)-N-[5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-iodophenyl] urea

15           The racemic compound was separated into its enantiomers using semi-preparative HPLC on a Pirkle dinitrobenzoylleucine column (5μ) [(250 x 21.4)mm] eluting with 4% methanol in 1-chlorobutane (including 1% acetic acid). 20ml/minute, λ = 305nm.

20           The free base was liberated then recrystallised from ethyl acetate to afford a colourless solid (600mg). mp 219-221°C. [α]<sub>D</sub><sup>23</sup> = -132° (c=0.2, methanol). Found: C, 54.23; H, 5.03; N, 12.54. C<sub>25</sub>H<sub>28</sub>IN<sub>5</sub>O<sub>2</sub> requires C, 53.87; H, 5.06; N, 12.56%.

25       EXAMPLE 49: (+)-N-[5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-iodophenyl] urea

          The title compound was obtained using the procedure described in Example 48. mp 220-222°C. [α]<sub>D</sub><sup>23</sup> = +132° (c=0.2, methanol). Found: C, 54.31; H, 4.99; N, 12.28. C<sub>25</sub>H<sub>28</sub>IN<sub>5</sub>O<sub>2</sub>  
30       requires C, 53.87; H, 5.06; N, 12.56%.

EXAMPLE 50: N-[3(R,S)-5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[phenyl] urea

The title compound was prepared using the procedure described in Example 31 but replacing m-tolylisocyanate with phenyl isocyanate. mp 214-215°C (tetrahydrofuran). MS,  $\text{Cl}^+$ ,  $m/z = 432$  for  $(\text{M}+\text{H})^+$ . Found: C, 69.78; H, 7.29; N, 14.62.  $\text{C}_{25}\text{H}_{29}\text{N}_5\text{O}_2 \cdot 0.5 \text{ C}_4\text{H}_8\text{O}$  requires C, 69.35; H, 7.11; N, 14.98%.

EXAMPLE 51: N-[3(R,S)-5-(2-Azabicyclo[2.2.2]octan-2-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl] urea

a) 2-Azabicyclo[2.2.2]octane

Anhydrous diethyl ether (150ml) was added to a stirred solution of 1M lithium aluminium hydride in diethyl ether (57ml). Powdered 3-isoquinuclidinone (9g, Organic Synthesis, Coll. Vol. V, 670) was added in portions over 15 minutes then the reaction mixture was heated at reflux for 5 hours. The mixture was cooled, quenched with saturated sodium chloride solution (5ml) then stirred for 30 minutes. Diethyl ether (150ml) was added then the reaction mixture was filtered, dried (potassium carbonate), evaporated to approximately 10ml volume then treated with n-hexane (20ml) and aged at -20°C for 1 hour. 2-Azabicyclo[2.2.2]octane was isolated (4.80g) as a colourless solid, mp 175-180°C.  $^1\text{H}$  NMR (360MHz,  $\text{CDCl}_3$ )  $\delta$  1.50-1.95 (9H, m), 2.84 (1H, s), 3.00 (2H, s), 3.38 (1H, broad s).

b) 5-(2-Azabicyclo[2.2.2]octan-2-yl)-1,3-dihydro-2H-1-methyl-1,4-benzodiazepin-2-one

The title compound was prepared from 1-methyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione and 2-azabicyclo[2.2.2]octane as described in Example 31. mp 140-142°C (diethyl ether/n-hexane). MS,  $\text{Cl}^+$ ,  $m/z = 284$  for  $(\text{M}+\text{H})^+$ . Found: C,

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70.62; H, 7.27; N, 14.41.  $C_{17}H_{21}N_3O \cdot 0.25H_2O$  requires C, 70.93; H, 7.53; N, 14.60%.

c) 5-(2-Azabicyclo[2.2.2]octan-2-yl)-1,3-dihydro-2H-1-methyl-3-oximido-1,4-benzodiazepin-2-one

5 The title compound was obtained from the foregoing benzodiazepine as described in Example 31. mp 264-266°C. MS,  $Cl^+$ ,  $m/z = 313$  for  $(M+H)^+$ . Found: C, 63.68; H, 6.44; N, 17.01.  $C_{17}H_{20}N_4O_2 \cdot 0.5H_2O$  requires C, 63.53; H, 6.59; N, 17.43%.

10 d) N-[3(R,S)-5-(2-Azabicyclo[2.2.2]octan-2-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl]urea

15 The title compound was prepared from the foregoing oxime as described in Example 31, Method B. mp 242-243°C (dec) (ethyl acetate). MS,  $Cl^+$ ,  $m/z = 432$  for  $(M+H)^+$ . Found: C, 69.95; H, 6.77; N, 16.25.  $C_{25}H_{29}N_5O_2$  requires C, 69.58; H, 6.77; N, 16.23%.

20 EXAMPLE 52: N-[3(R,S)-5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[4-fluoro-3-methylphenyl]urea

25 A stirred, cooled (4°C) solution of 3(R,S)-amino-5-(3-azabicyclo[3.2.2]nonan-3-yl)-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one (1.20g) in anhydrous tetrahydrofuran (15ml) was treated with triphosgene (388mg) and triethylamine (1.6ml). After 10 minutes 4-fluoro-3-methylaniline (576mg) was added. The cooling bath was removed and the reaction mixture was stirred at room temperature for 4 hours then evaporated to dryness. The residue was partitioned between chloroform (50ml) and water (50ml). The organic layer was separated, washed with water (30ml), dried (potassium carbonate) then evaporated to dryness. The solid obtained was recrystallised from hot ethyl acetate to afford the title compound (1.10g, 63%). mp 160-162°C.  $^1H$  NMR (360MHz,  $CDCl_3$ )  $\delta$  1.56-1.90 (8H, m), 1.94-2.02 (2H,

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m), 2.19 (3H, d,  $J = 2\text{Hz}$ ), 3.24-3.40 (2H, m), 3.41 (3H, s), 3.50-3.60 (2H, m), 5.28 (1H, d,  $J = 8\text{Hz}$ ), 6.57 (1H, d,  $J = 8\text{Hz}$ ), 6.85 (1H, dd,  $J_1 = J_2 = 9\text{Hz}$ ), 7.00-7.05 (1H, m), 7.17 (1H, s), 7.21-7.32 (3H, m), 7.47-7.54 (2H, m). Found: C, 65.27; H, 6.58; N, 14.45.

5  $\text{C}_{26}\text{H}_{30}\text{FN}_5\text{O}_2 \cdot 0.75\text{H}_2\text{O}$  requires C, 65.46; H, 6.66; N, 14.68%.

EXAMPLE 53: (-)-N-[5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[4-fluoro-3-methylphenyl] urea Hydrochloride

10 The racemic compound (Example 52, 620mg) was separated into its enantiomers using semi-preparative HPLC on a Pirkle dinitrobenzoylleucine column ( $5\mu$ ) [(250 x 21.4)mm] eluting with 5% methanol in 1-chlorobutane (including 1% acetic acid). 20ml/minute,  $\lambda = 305\text{nm}$ .

15 The fractions from peak A were evaporated to dryness and the free base liberated (255mg). The hydrochloride salt had mp 221-223°C (acetonitrile/ethyl acetate).  $[\alpha]^{23^\circ\text{C}}_{\text{D}} = -248^\circ$  ( $c=0.2$ , methanol). MS,  $\text{CI}^+$ ,  $m/z = 464$  for  $(\text{M}+\text{H})^+$  of free base. Found: C, 61.41; H, 6.22; N, 13.46.  $\text{C}_{26}\text{H}_{30}\text{FN}_5\text{O}_2 \cdot \text{HCl} \cdot 0.5\text{H}_2\text{O}$  requires C, 61.35; H, 6.34; N, 13.76%.

20

EXAMPLE 54: (+)-N-[5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[4-fluoro-3-methylphenyl] urea Hydrochloride

25 Obtained using the procedure described in Example 53. mp 221-223°C (acetonitrile/ethyl acetate).  $[\alpha]^{23^\circ\text{C}}_{\text{D}} = +240^\circ$  ( $c=0.2$ , methanol). Found: C, 61.73; H, 6.20; N, 13.60.  $\text{C}_{26}\text{H}_{30}\text{FN}_5\text{O}_2 \cdot \text{HCl} \cdot 0.5\text{H}_2\text{O}$  requires C, 61.35; H, 6.34; N, 13.76%.

30 EXAMPLE 55: (-)-N-[5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-trifluoromethylphenyl] urea Hydrochloride



The racemic compound (Example 42, 400mg) was separated into its enantiomers as described in Example 53. mp 215-217°C (acetonitrile/ethyl acetate).  $[\alpha]^{23}_{\text{D}} = -216^{\circ}$  (c=0.2, methanol). MS,  $\text{Cl}^+$ ,  $m/z = 500$  for  $(\text{M}+\text{H})^+$  of free base. Found: C, 57.76; H, 5.18; N, 12.79.  $\text{C}_{28}\text{H}_{28}\text{F}_3\text{N}_5\text{O}_2 \cdot \text{HCl} \cdot 0.25\text{H}_2\text{O}$  requires C, 57.78; H, 5.50; N, 12.96%.

EXAMPLE 56: (+)-N-[5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-(3-trifluoromethylphenyl) urea Hydrochloride

Obtained using the procedure described in Example 53. mp 209-212°C (acetonitrile/ethyl acetate).  $[\alpha]^{23}_{\text{D}} = +212^{\circ}$  (c=0.2, methanol). Found: C, 53.25; H, 5.32; N, 11.86.  $\text{C}_{28}\text{H}_{28}\text{F}_3\text{N}_5\text{O}_2 \cdot \text{HCl} \cdot 3\text{H}_2\text{O}$  requires C, 52.93; H, 5.88; N, 11.87%.

EXAMPLE 57: N-[3(R,S)-2,3-Dihydro-1-methyl-5-(cis-octahydroisoindol-2-yl)-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-(3-methylphenyl) urea  
a) Cis-Octahydroisoindole

Cis-4-cyclohexene-1,2-dicarboximide (10.9g) was hydrogenated over 10% palladium on carbon (1g) in absolute ethanol (420ml) at 50 psi for 10 minutes. The mixture was filtered then evaporated to give cis-cyclohexane-1,2-dicarboximide (10.6g). To anhydrous diethyl ether (200ml) was cannulated under nitrogen a 1M diethyl ether solution (200ml) of lithium aluminium hydride. To the foregoing solution, under reflux, was added cis-cyclohexane-1,2-dicarboximide (10.6g) portionwise over 10 minutes. The reaction mixture was heated to reflux for 3 hours. After cooling to 0°C, water (7ml) was added followed by 4N sodium hydroxide (7.6ml) and water (23ml). The white suspension was stirred whilst warming to room temperature. The solid was removed by filtration then the

filtrate dried (sodium sulphate) and evaporated to give a cream oil.

b) 1,3-Dihydro-1-methyl-5-(cis-octahydroisindol-2-yl)-2H-1,4-benzodiazepin-2-one

5        A solution of phosphorus pentachloride (6.15g) in dichloromethane (250ml) was added dropwise over 30 minutes to a stirred solution of 1-methyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione (4.56g) in dichloromethane (150ml). The solution was stirred at room temperature for 2 hours, the  
10       solvent evaporated *in vacuo* and the residue azeotroped with toluene. The dark solid was re-dissolved in dichloromethane (200ml), cooled to 4°C and a solution of crude *cis*-octahydroisindole (3g) and triethylamine (6.6ml) in dichloromethane (100ml) was added over 30 minutes. The cooling  
15       bath was removed and the reaction mixture was stirred for 2 hours, then washed sequentially with 10% potassium carbonate and brine (twice). The organic layer was separated, treated with potassium carbonate, silica (Kieselgel) and decolourizing charcoal. The mixture was filtered then evaporated to dryness  
20       and purified by column chromatography on silica using dichloromethane → 10% methanol/dichloromethane (containing 1% ammonia) to afford the title compound (3.3g). mp > 128°C (dec.). <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.16-1.72 (8H, m), 2.04-2.18 (1H, m), 2.3-2.43 (1H, m), 2.9-3.2 (2H, m), 3.36 (3H, s), 3.54 (1H, d, J = 12Hz), 3.5-3.76 (2H, m), 4.23 (1H, d, J = 12Hz), 7.19-7.32  
25       (2H, m), 7.44-7.52 (2H, m).

c) 1,3-Dihydro-1-methyl-5-(cis-octahydroisindol-2-yl)-2H-3-oximido-1,4-benzodiazepin-2-one

30       Potassium t-butoxide (2.94g) was added in portions to a stirred, cooled (-25°C) solution of 1,3-dihydro-1-methyl-5-(*cis*-octahydroisindol-2-yl)-2H-1,4-benzodiazepin-2-one (3.2g) in anhydrous toluene (110ml) under a nitrogen atmosphere. After stirring at -25°C for 50 minutes isopentyl nitrite (1.6ml) was

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added. The reaction mixture was stirred at -25°C for 6 hours, then isopentyl nitrite (0.8ml) was added followed sequentially by potassium t-butoxide (300mg) after 18 hours, isopentyl nitrite (0.4ml) after a further 30 minutes and finally isopentyl nitrite (1.6ml) after a further 5 hours. The mixture was then stirred at -25°C overnight. Whilst warming to room temperature the reaction mixture was treated with water (30ml) containing citric acid (2.3g) and diethyl ether (40ml) then stirred for 1 hour. The precipitate was collected to afford the oxime (2.3g). mp 236-238°C. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.08-1.84 (8H, m), 2.12-2.56 (2H, m), 3.0-4.0 (4H, m), 3.41 and 3.45 (3H, each s), 7.18-7.64 (4H, m).

d) 1,3-Dihydro-1-methyl-5-(cis-octahydroisoindol-2-yl)-2H-3-(O-(ethylaminocarbonyl)oximido)-1,4-benzodiazepin-2-one

The foregoing oxime (2.3g), ethylisocyanate (2.8ml) and triethylamine (1ml) were heated at 65°C in anhydrous tetrahydrofuran (150ml) for 18 hours. The solvent was evaporated and the residue was purified by column chromatography on silica using dichloromethane → 3% methanol/dichloromethane to afford a white foam (2.8g, mixture of E/Z isomers). mp 175-180°C. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.08-1.78 (8H, m), 1.13 (3H, t, J = 7Hz), 2.06-2.37 (2H, m), 2.90-3.12 (1H, m), 3.25 (2H, q, J = 7Hz), 3.44 and 3.45 (3H, each s), 3.53-3.80 (3H, m), 6.20-6.30 and 6.36-6.46 (1H, each m), 7.20-7.55 (4H, m).

e) 3(R,S)-Amino-1,3-dihydro-1-methyl-5-(cis-octahydroisoindol-2-yl)-2H-1,4-benzodiazepin-2-one

The product of part a) (2.4g) was hydrogenated at 45 psi in methanol (160ml) over 10% palladium on carbon (1g) for 3 hours at room temperature. The mixture was filtered then evaporated to dryness to afford the title amine (2g).

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f) N-[3(R,S)-2,3-Dihydro-1-methyl-5-(cis-octahydroisoindol-2-yl)-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl]urea

The foregoing amine (2g) in anhydrous tetrahydrofuran (5ml) was treated with m-tolylisocyanate (0.72ml). After standing for 5 minutes 1 drop of dichloromethane was added. After ageing at 4°C for 18 hours the precipitate was collected to afford the title compound as a free base (2.2g). mp > 156°C (dec.). <sup>1</sup>H NMR (360MHz, DMSO) δ 1.12-1.64 (8H, m), 1.96-2.09 (1H, m), 2.21 (3H, s), 2.30-2.36 (1H, m), 2.74-3.1 (1H, m), 3.27-3.37 (1H, m), 3.31 (3H, s), 3.45-3.62 (2H, m), 4.94 (1H, d, J = 8Hz), 6.68-7.67 (8H, m), 6.91 (1H, d, J = 8Hz), 8.79 (1H, s). Found: C, 65.40; H, 6.70; N, 14.83. C<sub>26</sub>H<sub>31</sub>N<sub>5</sub>O<sub>2</sub>·1.7H<sub>2</sub>O requires C, 65.57; H, 7.28; N, 14.70%.

EXAMPLE 58: (-)-N-[2,3-Dihydro-1-methyl-5-(cis-octahydroisoindol-2-yl)-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl]urea hydrochloride

The racemic compound (Example 57, 1g) was separated into its enantiomers using semi-preparative chiral HPLC on a Pirkle dinitrobenzoylleucine column (5μ) [(250 x 21.4)mm] eluting with ethanol/hexane (1:1), flow rate 20ml/minute, U.V. detection at 310nm.

The hydrochloride salt (350mg) had mp > 190°C (dec.). MS, CI<sup>+</sup>, m/z = 446 for (M+H)<sup>+</sup>. [α]<sub>D</sub><sup>25</sup> = -107.5° (c=0.2, methanol). Found: C, 61.65; H, 6.96; N, 13.33. C<sub>26</sub>H<sub>31</sub>N<sub>5</sub>O<sub>2</sub>·HCl·1.5H<sub>2</sub>O·0.1 C<sub>4</sub>H<sub>8</sub>O requires C, 61.42; H, 6.99; N, 13.57%. HPLC (spherisorb ODS2, 70% acetonitrile/30% of 0.2% triethylamine in water and orthophosphoric acid to pH = 3): 98.5% chemically pure.

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**EXAMPLE 59:** (+)-N-[2,3-Dihydro-1-methyl-5-(cis-octahydroisoindol-2-yl)-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-(3-methylphenyl)urea hydrochloride

The title compound was obtained (360mg) using the procedure described in Example 58. The hydrochloride salt had mp > 190°C (dec.). MS, CI<sup>+</sup>, m/z = 446 for (M+H)<sup>+</sup>.  $[\alpha]_{25}^{25} = +109^\circ$  (c=0.2, methanol). Found: C, 62.10; H, 7.02; N, 13.50. C<sub>26</sub>H<sub>31</sub>N<sub>5</sub>O<sub>2</sub>·HCl·1.2H<sub>2</sub>O requires C, 62.00; H, 6.88; N, 13.90%. HPLC (spherisorb ODS2, 70% acetonitrile/30% of 0.2% triethylamine in water and orthophosphoric acid to pH = 3): > 99% chemically pure.

**EXAMPLE 60:** N-[3(R,S)-5-(N-Cyclohexyl-N-methylamino)-2,3-dihydro-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl]-N'-(3-methylphenyl)urea

a) 5-(N-Cyclohexyl-N-methylamino)-2-oxo-1-propyl-1,4-benzodiazepine

Prepared analogously to Example 1a) from 1-propyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione (10.0g) and N-methylcyclohexylamine (15.6g) and purified by flash chromatography, eluted with 2% methanol/0.5% 0.88 ammonia solution/dichloromethane then 5% methanol/0.5% 0.88 ammonia solution/dichloromethane. <sup>1</sup>H NMR (DMSO) δ 0.68 (3H, t, J = 7.3Hz), 1.84-2.04 (3H, m), 2.72 (3H, s), 3.40 (1H, d, J = 12.2Hz), 3.54 (1H, m), 3.88 (1H, d, J = 12.2Hz), 4.22 (1H, m), 7.34 (1H, m), 7.50 (1H, d, J = 7.43Hz), 7.60 (2H, m).

b) 5-(N-Cyclohexyl-N-methylamino)-3-oximino-2-oxo-1-propyl-1,4-benzodiazepine

Prepared analogously to Example 1b) from product from step (a) (5g). The product was purified using flash silica chromatography, eluting with 0.5% 0.88 ammonium solution/2% methanol/dichloromethane followed by chromatography on an alumina column, eluting with 2% methanol/dichloromethane

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followed by 5% methanol/dichloromethane.  $^1\text{H}$  NMR (DMSO)  $\delta$  0.52-2.06 (16H, m), 2.60-2.92 (3H, m), 3.60 (1H, m), 4.26 (1H, m), 7.22-7.66 (14H, m), 9.84 and 10.02 (1H, 2 x s).

5 c) N-[3(R,S)-5-(N-Cyclohexyl-N-methylamino)-2,3-dihydro-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl] urea

The product from step b) (2.31g) was dissolved in acetic acid (40ml), with activated zinc (8.83g) and trifluoroacetic acid (5.21ml). The reaction was heated at 40°C for 8h with vigorous stirring, then cooled to room temperature, filtered through hiflo, and washed through with acetic acid (2 x 20ml). The solvent was removed in vacuo, the resulting oil was azeotroped with toluene and dried under high vacuum for 30 min to give a yellow foam. The foam was redissolved in tetrahydrofuran (50ml), and triethylamine (1.0ml) was added followed by m-tolylisocyanate (0.87ml). The reaction was stirred at room temperature for 2h then concentrated under vacuum. The residue was redissolved in dichloromethane (100ml), washed with saturated sodium hydrogen carbonate solution (100ml), separated and the aqueous phase was reextracted with dichloromethane (2 x 25ml). The combined organic layers were washed with brine (50ml), dried (sodium sulphate) and the solvent was removed in vacuo to give a solid which was purified by flash column chromatography with 0.5% 0.88 ammonia solution/dichloromethane as the eluant on a Lobar column. Mp = 118°C (uncorr);  $^1\text{H}$  NMR (DMSO)  $\delta$  0.70 (3H, t,  $J$  = 7.4Hz), 0.90-1.90 (13H, m), 2.23 (3H, s), 2.68 (3H, s), 3.64 (1H, m), 4.26 (1H, m), 4.90 (1H, d,  $J$  = 8.4Hz), 6.71 (1H, d,  $J$  = 8.0Hz), 6.92 (1H, d,  $J$  = 8.6Hz), 7.12 (2H, m), 7.16 (1H, s), 7.38 (1H, m), 7.51 (1H, d,  $J$  = 7.5Hz), 7.64 (2H, m); MS (CI) m/e 462 [MH] $^+$ . Anal. Found C, 66.38; H, 7.72; N, 14.07.  $\text{C}_{27}\text{H}_{35}\text{N}_5\text{O}_2 \cdot 1.5\text{H}_2\text{O}$ , requires C, 66.37; H, 7.84; N, 14.33%.

EXAMPLE 61: (-)-5-(N-Cyclohexyl-N-methylamino)-2,3-dihydro-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl-N'-[3-methylphenyl] urea

The racemate (430mg) of Example 60 was separated using preparative chiral HPLC with a dinitrobenzoyl leucine column (250 x 20 mm i.d. 5µm) using 94:5:1 1-chlorobutane:methanol:acetic acid as the mobile phase (with a flow rate of 20ml/min and UV detection at 330nm). The two enantiomers were efficiently separated into Peak A (eluted first) and peak B (eluted second).

Peak A was evaporated in vacuo, and was partitioned between dichloromethane and sodium carbonate solution. The organic phases were dried (MgSO<sub>4</sub>), evaporated in vacuo and the residue obtained was triturated with diethyl ether and the resulting solid was collected by filtration to give: Peak A (127mg). Mp = 121-123°C; <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 0.69 (3H, t, J = 7.4Hz), 0.9-1.90 (13H, m), 2.21 (3H, s), 2.66 (3H, s), 3.64 (1H, m), 4.25 (1H, m), 4.89 (1H, d, J = 8.4Hz), 6.70 (1H, d, J = 8.0Hz), 6.94 (1H, d, J = 7.5Hz), 7.10 (2H, m), 7.16 (1H, s), 7.37 (1H, m), 7.50 (1H, d, J = 7.5Hz), 7.65 (2H, m), 8.80 (1H, s); MS (CI) m/e 462 [MH]<sup>+</sup>. Anal. Found. C, 68.38; H, 7.74; N, 14.29. C<sub>27</sub>H<sub>35</sub>N<sub>5</sub>O<sub>2</sub>·0.85 H<sub>2</sub>O requires C, 68.00; H, 7.76; N, 14.69. [α]<sub>D</sub><sup>22</sup> -114° (C=0.1, MeOH). Purity A:B = > 99%.

EXAMPLE 62: (+) 5-(N-Cyclohexyl-N-methylamino)-2,3-dihydro-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl-N'-[3-methylphenyl] urea

Peak B from Example 61 was treated in the same way as Peak A Example 61. Mp = 126-127°C; <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 0.69 (3H, t, J = 7.4Hz), 0.9-1.90 (13H, m), 2.21 (3H, s), 2.66 (3H, s), 3.62 (1H, m), 4.25 (1H, m), 4.89 (1H, d, J = 8.4Hz), 6.70 (1H, d, J = 8.0Hz), 6.94 (1H, d, J = 7.5Hz), 7.00 (2H, m), 7.17 (1H, s), 7.38 (1H, m), 7.50 (1H, d, J = 7.5Hz), 7.65 (2H,

m), 8.80 (1H, s); MS (CI) m/e 462 [MH]<sup>+</sup>. Anal. Found. C, 69.93; H, 7.54; N, 14.62. C<sub>27</sub>H<sub>35</sub>N<sub>5</sub>O<sub>2</sub>·0.2 H<sub>2</sub>O requires C, 69.71; H, 7.67; N, 15.05%. [α]<sub>D</sub><sup>22</sup> +108° (C=0.1, MeOH). Purity B:A = > 96:4.

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EXAMPLE 63: N-[3(R,S)-5-(N-Cyclohexyl-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl] urea

Prepared as for Example 60 parts a, b, and c, from 1-methyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione and recrystallised from methanol, water. Mp 145-147°C. <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 0.99 (10H, m), 2.21 (3H, s), 2.65 (3H, s), 3.31 (4H, m), 4.92 (1H, d, J = 8.4Hz), 6.70 (1H, d, J = 8.0Hz), 6.93 (1H, d, J = 7.5Hz), 7.09 (2H, m), 7.17 (1H, s), 7.36 (1H, m), 7.49-7.69 (3H, m), 8.80 (1H, s); MS (CI) m/e 434 [MH]<sup>+</sup>. Anal. Found. C, 67.22; H, 7.23; N, 15.29. C<sub>25</sub>H<sub>31</sub>N<sub>5</sub>O<sub>2</sub>·0.75H<sub>2</sub>O requires C, 67.17; H, 7.33; N, 15.67%.

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EXAMPLE 64: (-) 5-(N-Cyclohexyl-N-methylamino)-2,3-dihydro-2-oxo-1-methyl-1H-1,4-benzodiazepin-3-yl-N'-[3-methylphenyl] urea. Hydrochloride

Separated from the racemate of Example 63 by chiral HPLC as for Example 61. Peak A free base was dissolved in dichloromethane. Ethereal hydrogen chloride was added and after 5 minutes the solvent was removed in vacuo. The resulting oil was crystallised from dichloromethane/ether. Mp 193-195°C. <sup>1</sup>H (360MHz, D<sub>6</sub>-DMSO, trifluoroacetic acid) δ 0.95-1.95 (10H, m), 2.23 (3H, s), 3.12 (3H, s), 3.43 (4H, m), 5.39 (1H, m), 6.76 (1H, d, J = 7.2Hz), 7.11-7.90 (7H, m). MS (CI) m/e 434 [MH]<sup>+</sup>. Anal. Found. C, 60.45; H, 7.02; N, 14.05. C<sub>25</sub>H<sub>31</sub>N<sub>5</sub>O<sub>2</sub>·HCl·1.5H<sub>2</sub>O requires C, 60.41; H, 7.02; N, 14.35%. [α]<sub>D</sub><sup>22</sup> -195° (c = 0.1, MeOH). Purity A:B = >99%.

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EXAMPLE 65: (+)-5-(N-Cyclohexyl-N-methylamino)-2,3-dihydro-2-oxo-1-methyl-1,4-benzodiazepin-3-yl-N'-[3-methylphenyl] urea. Hydrochloride

Separated from the racemate of Example 63 by chiral HPLC as for Example 61. Peak B (eluted second) was treated as in Example 64 to yield the desired hydrochloride (90mg). Mp 194-196°C. <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO + trifluoroacetic acid) δ 0.95-1.95 (10H, m), 2.24 (3H, s), 3.12 (3H, s), 3.43 (4H, m), 5.39 (1H, m), 6.76 (1H, d, J = 7.5Hz), 7.06-7.86 (7H, m), 9.20 (1H, s); MS (CI) m/e 434 [MH]<sup>+</sup>. Anal. Found. C, 58.28; H, 6.82; N, 13.47. C<sub>25</sub>H<sub>31</sub>N<sub>5</sub>O<sub>2</sub>.HCl.2.35H<sub>2</sub>O requires C, 58.61; H, 7.22; N, 13.67%. [α]<sub>D</sub><sup>22</sup> +154° (C=0.1, MeOH). Purity B:A = > 95%.

EXAMPLE 66: N-[3(R,S)-5-(N-Cycloheptyl-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl] urea

Prepared analogously to Example 60 from N-methylcycloheptylamine. Mp = 135°C (uncorr); <sup>1</sup>H NMR (DMSO) δ 1.10 (1H, m), 1.20-1.50 (7H, m), 1.50-1.84 (4H, m), 1.91 (1H, m), 2.22 (3H, s), 2.63 (3H, s), 3.31 (3H, s), 4.94 (1H, d, J = 8.0Hz), 6.70 (1H, d, J = 6.9Hz), 6.94 (1H, d, J = 8.4Hz), 7.09 (2H, m), 7.17 (1H, s), 7.37 (1H, t, J = 6.9Hz), 7.51 (1H, dd, J = 7.8 and 1.3Hz), 7.62 (2H, m), 8.82 (1H, s); MS (CI) m/e 448 [MH]<sup>+</sup>. Anal. Found. C, 70.02; H, 7.41; N, 15.60. C<sub>26</sub>H<sub>33</sub>N<sub>5</sub>O<sub>2</sub> requires C, 69.77; H, 7.43; N, 15.65%.

EXAMPLE 67: (-)-5-(N-Cycloheptyl-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl-N'-[3-methylphenyl] urea. Hydrochloride

a) The racemate (700mg) of Example 66 was separated using preparative chiral HPLC with a dinitrobenzoylleucine column (250 x 20mm i.d, 5 μM) using 89:10:1

1-chlorobutane:methanol:acetic acid as the mobile phase, with a flow rate of 20ml/minute and u.v. detection of 330nm.

Peak A was evaporated in vacuo and redissolved in the minimum of dichloromethane. The hydrochloride salt has formed by adding a saturated solution of hydrogen chloride in ether (5ml). The resulting solution was triturated with ether, filtered and dried under high vacuum. Mp. 172=174°C; <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO, V.T. α 353K) δ 1.04-2.12 (13H, m), 2.24 (3H, s), 3.04 (3H, s), 3.38 (3H, s), 5.32 (1H, d, J = 7.6Hz), 6.72 (1H, d, J = 7.6Hz), 7.04-7.26 (4H, m) 7.52 (1H, t, J = 7.6Hz), 7.70 (2H, m), 7.82 (1H, t, J = 7.3Hz), 9.24 (1H, s(b)); MS (CI) m/e 448 [MH]<sup>+</sup>. Anal. Found. C, 62.44; H, 7.29; N, 13.71. C<sub>26</sub>H<sub>33</sub>N<sub>5</sub>O<sub>2</sub>.HCl requires C, 62.20; H, 7.23; N, 13.95. [α]<sub>D</sub><sup>22</sup> = -210° (c=1mgm<sup>-1</sup>, MeOH). Purity A:B > 99%.

**EXAMPLE 68:** (+)-5-(N-Cycloheptyl-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl-N'-[3-methylphenyl] urea. Hydrochloride

Peak B from Example 67 was treated in the same way as peak A to give the required product. Mp 173-175°C; <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO, V.T. α 353K) δ 1.06-2.14 (13H, m), 2.24 (3H, s), 3.05 (3H, s), 3.38 (3H, s), 5.33 (2H, d, J = 7.6Hz), 6.74 (1H, d, J = 7.2Hz) 7.04-7.26 (4H, m), 7.54 (1H, t, J = 7.5Hz), 7.63-7.74 (2H, m), 7.82 (1H, t, J = 7.5Hz), 9.25 (1H, s(b)); MS (CI) m/e 448 [MH]<sup>+</sup>. Anal. Found. C, 62.36; H, 7.26; N, 13.53. C<sub>26</sub>H<sub>33</sub>N<sub>5</sub>O<sub>2</sub>.HCl requires C, 62.20; H, 7.23; N, 13.95. [α]<sub>D</sub><sup>22</sup> = +172° (c = 1mgm<sup>-1</sup>, MeOH). Purity B:A = 96.2%

**EXAMPLE 69:** N-[3(R,S)-5-(N-Cycloheptyl-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[5-indanyl] urea

a) (±)-N-[3-amino-5-(N-cycloheptyl-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepine. (TFA salt)

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To a solution of 5-(N-cycloheptyl-N-methylamino)-1-methyl-3-oximino-2-oxo-1,4-benzodiazepine (1.00g,) in acetic acid (40ml) was added activated zinc (3.99g) and trifluoroacetic acid (3.48g). The reaction was stirred at 40°C for 30 minutes, cooled to room temperature, filtered through hiflo, and washed with acetic acid (2 x 20ml). The solvent was removed in vacuo, and the resulting oil was azeotroped with toluene and dried under high vacuum.

b) N-[3(R,S)-5-(N-Cycloheptyl-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[5-indanyll urea

5-aminoindane (0.41g) was dissolved in tetrahydrofuran (50ml) and cooled (0°C) under nitrogen. Triphosgene (0.31g) was added and the reaction stirred vigorously (2 minutes). Triethylamine (0.92g) was added and the reaction stirred for a further 30 minutes.

A solution of the product from part a) and triethylamine (sufficient to take solution to pH9) in tetrahydrofuran (25ml) was added dropwise and the reaction allowed to stir overnight. The solvent was removed in vacuo, and the reaction mixture redissolved in dichloromethane (100ml). This solution was washed with saturated sodium bicarbonate solution (50ml), reextracted with dichloromethane (3 x 25ml) and the combined organics washed with brine (50ml). The solution was dried over sodium sulphate and the solvent removed in vacuo to give an oil that was purified by column chromatography with 0.2% 0.88 ammonia solution/dichloromethane then by 0.2% 0.88 ammonia solution/2% methanol/dichloromethane as the eluent. The product was recrystallised from ethyl acetate/60-80 petrol. Mp 183-185°C. <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO, V.T. α 353K) δ 0.80-1.80 (11H, m), 1.86-2.04 (3H, m), 2.65 (3H, s), 2.74 (4H, q, J = 7.0Hz), 3.30 (3H, s), 3.59 (1H, m), 4.94 (1H, d, J = 7.1Hz), 6.74 (1H, d, J = 8.4Hz), 7.02 (2H, m), 7.22 (1H, s), 7.34 (1H, t, J =

8.4Hz), 7.48 (1H, m), 7.52 (1H, m), 7.60 (1H, m), 8.60 (1H, s).  
 MS (CI) m/e 474 [MH]<sup>+</sup>. Anal. Found. C, 71.69; H, 7.86; N,  
 14.14. C<sub>28</sub>H<sub>35</sub>N<sub>5</sub>O<sub>2</sub>·0.3C<sub>6</sub>H<sub>4</sub> requires C, 71.66; N, 7.91; N, 14.02%

5 EXAMPLE 70: (-)-5-(N-Cycloheptyl-N-methylamino)-2,3-  
dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl-N'-[5-indanyl]  
urea Hydrochloride

10 a) The racemate of Example 69 (600mg) was separated  
 using preparative chiral HPLC with a dinitrobenzoylleucine  
 column (250 x 20mm i.d, 5µm) using 70% ethanol in hexane as  
 eluent at a flow rate of 20ml/min and u.v. detection at 330nm.

15 Peak A was concentrated in vacuo and redissolved in  
 dichloromethane (~2ml). A saturated solution of hydrogen  
 chloride in dry diethyl ether (5ml) was added and the resulting  
 20 suspension was triturated with more diethyl ether (20ml). The  
 product was collected by filtration. Mp 181-187°C dec; <sup>1</sup>H NMR  
 (360MHz, DMSO) δ 1.20-2.12 (14H, m), 2.76 (4H, q, J = 7.0Hz),  
 2.93-3.12 (3H, 2s, CH<sub>3</sub> restricted rotation), 3.42 (3H, s), 3.62 and  
 4.18 (1H, 2m), 5.36 (1H, m), 7.05-7.90 (8H, m), 9.48-9.53 (1H,  
 2s). 10.17 and 10.32 (1H, 2br s); MS (CI) m/e 474 [MH]<sup>+</sup>. Anal.  
 Found C, 62.83; H, 7.19; N, 13.07. C<sub>28</sub>H<sub>35</sub>N<sub>5</sub>O<sub>2</sub>·HCl·1.5H<sub>2</sub>O  
 requires C, 62.61; H, 7.32; N, 13.04%. [α]<sub>D</sub><sup>25</sup> -175° (c = 0.1,  
 MeOH). Purity A:B > 99%.

25 EXAMPLE 71: (+)-[5-(N-Cycloheptyl-N-methylamino)-2,3-  
dihydro-1-ethyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[5-indanyl]  
urea Hydrochloride

30 Prepared analogously to Example 70. m.p. 181-187°C dec;  
<sup>1</sup>H NMR (360MHz, DMSO) δ 1.20-2.19 (14H, m), 2.76 (4H, q, J =  
 7.0Hz), 2.93 and 3.12 (3H, 2s, CH<sub>3</sub> restricted rotation), 3.42 (3H,  
 s), 3.62 and 4.18 (1H, 2m), 5.36 (1H, m). 7.05-7.90 (8H, m), 9.40  
 and 9.42 (1H, 2s), 10.10 and 10.26 (1H, 2br s); MS (CI) m/e 474  
 [MH]<sup>+</sup>. Anal. Found C, 62.83; H, 7.20; N, 13.06.

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$C_{28}H_{35}N_5O_2 \cdot HCl \cdot 1.5H_2O$  requires C, 62.61; H, 7.32; N, 13.04%.  
 $[\alpha]_D^{22} +197^\circ$  (c=0.1, MeOH). Purity B:A > 99%.

**EXAMPLE 72: N-[3(R,S)-5-(N-Benzyl-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl]urea**

To a solution of 5-(N-benzyl-N-methylamino)-3-oximino-2-oxo-1-methyl-1,4-benzodiazepine (prepared as for Example 1 parts a and b, from 1-methyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione and N-methylbenzylamine) in methanol was added rhodium on carbon (600mg) and the resultant mixture was hydrogenated at 50psi at 60°C for 5h. The reaction mixture was allowed to cool, filtered and concentrated in vacuo. The residue was dissolved in tetrahydrofuran, cooled to 0°C and m-tolylisocyanate added. This mixture was stirred at room temperature for 12 hours, solvent removed in vacuo and the residue purified by flash column chromatography with 0.5% 0.88 ammonia solution, methanol and dichloromethane as the eluent, to yield the product which was recrystallised from dichloromethane, ethyl acetate (1:1). Mp 172-174°C.  $^1H$  NMR (360MHz,  $D_6$ -DMSO)  $\delta$  2.21 (3H, s), 2.74 (3H, s), 4.26 and 4.55 (2H, dd,  $J$  = 15.8Hz), 5.00 (1H, d,  $J$  = 8.4Hz), 6.70 (1H, d,  $J$  = 8.0Hz), 6.96-7.76 (12H, m), 8.81 (1H, s); MS (CI) m/e 442 (MH)<sup>+</sup>. Anal. Found C, 70.86; H, 6.39; N, 15.85%  $C_{26}H_{27}N_5O_2$  requires C, 70.73; H, 6.16; N, 15.86%.

**EXAMPLE 73: N-[3(R,S)-5-(N-(4-N-Methylpiperidinyl)-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl]urea**

Prepared analogously to Example 60 from 1-methyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione and N-methyl-(4-methylamino)piperidine. Mp = 146°C (uncorr);  $^1H$

NMR (DMSO)  $\delta$  1.24 (1H, m), 1.60-1.90 (6H, m), 2.12 (3H, s) 2.21 (3H, s), 2.65 (3H, s), 2.75 (1H, m), 2.82 (1H, m), 3.32 (3H, s), 4.92 (1H, d,  $J$  = 8.4Hz), 6.70 (1H, d,  $J$  = 7.1Hz), 6.95 (1H, d,  $J$  = 8.4Hz), 7.09 (2H, m), 7.17 (1H, s), 7.38 (1H, m), 7.51 (1H, dd,  $J$  = 1.4 + 7.8Hz), 7.62 (2H, m), 8.82 (1H, s); MS (CI)  $m/e$  449 [MH]<sup>+</sup>.  
5 Anal. Found: C, 63.37; H, 7.04; N, 17.46.  $C_{25}H_{32}N_6O_2 \cdot 1.3H_2O$  requires C, 63.62; H, 7.39; N, 17.81%.

10 EXAMPLE 74: N-[3(R,S)-5-(N-Cyclohexylmethyl-N-methylamino)-2,3-dihydro-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl]urea

Prepared as described in Example 60 from N-methylcyclohexylamine and 1-methyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione; mp 218-225°C. <sup>1</sup>H NMR (DMSO)  $\delta$   
15 0.31 (1H, m), 0.66 (1H, m), 0.96-1.54 (9H, m), 2.21 (3H, s), 2.81 (3H, s), 2.92 (1H, m), 3.16 (1H, m), 3.30 (3H, s), 4.94 (1H, d,  $J$  = 8.4Hz), 6.70 (1H, d,  $J$  = 7.0Hz), 6.91 (1H, d,  $J$  = 8.4Hz), 7.05-7.65 (7H, m), 8.81 (1H, s); MS (CI)  $m/e$  448 [MH]<sup>+</sup>. Anal. Found C, 65.59; H, 7.44; N, 15.46.  $C_{26}H_{33}N_5O_2$  requires C, 69.77; H, 7.47; N, 15.65%.  
20

EXAMPLE 75: N-[3(R,S)-5-(N,N-Di-n-propylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl]urea

25 Prepared as for Example 60, using di-n-propylamine in place of N-methylcyclohexylamine and recrystallized from ethyl acetate and hexane. Mp 164-166°C. <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO-TFA)  $\delta$  0.60 (3H, t,  $J$  = 7.3Hz), 0.99 (3H, t,  $J$  = 7.4Hz), 1.57 (2H, m), 1.73 (2H, m), 2.25 (3H, s), 3.43 (5H, m), 3.88 (2H, m), 5.40 (1H, d,  $J$  = 6.3Hz), 6.78 (1H, d,  $J$  = 7.1Hz), 7.35-7.70  
30 (8H, m), 9.30 (1H, s) MS (CI)  $m/e$  422 [MH]<sup>+</sup>. Anal. Found: C, 68.33; H, 7.44; N, 16.27%.  $C_{24}H_{31}N_5O_2$  requires C, 68.38; H, 7.41; N, 16.61%.

EXAMPLE 76: N-[3(R,S)-5-(N-Cyclopentyl-N-ethylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl]urea

5 Prepared as for Example 72, but using N-ethylcyclopentylamine in place of N-methylbenzylamine and recrystallized from ethyl acetate hexane. Mp = 252-255°C, <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 0.70-1.60 (11H, m), 2.21 (3H, s), 2.91-3.90 (6H, m), 5.37 (1H, d, J = 8.4Hz), 6.72 (1H, d, J = 8.0Hz), 6.92 (1H, d, J = 7.5Hz), 7.10 (2H, m), 7.29-7.63 (5H, m), 10.24 (1H, s). Anal. Found: C, 69.70; H, 7.21; N, 15.41%. C<sub>25</sub>H<sub>31</sub>N<sub>5</sub>O<sub>2</sub> · 0.15C<sub>6</sub>H<sub>14</sub> requires C, 69.68; H, 7.47; N, 15.69%.

15 EXAMPLE 77: N-[3(R,S)-5-(N-(4,4-Dimethylcyclohexyl)-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl]urea

a) N-Methyl-4,4-dimethylcyclohexylamine

20 To a solution of 4,4-dimethylcyclohexanone (25.2g) in dry methanol under an atmosphere of nitrogen was added methylamine hydrochloride (13.2g) and 3Å mol sieves (1g). The reaction mixture was stirred for 1hr then sodium cyanoborohydride (12.7g) added portionwise. The mixture was stirred for 17hrs. A saturated solution of hydrogen chloride in methanol (200ml) was added and the reaction mixture stirred for 25 1hr the filtered through hyflo and concentrated in vacuo. The residue was partitioned between 1N sodium hydroxide (300ml) and dichloromethane (200ml). The layers were separated and the aqueous re-extracted with dichloromethane (2 x 200ml). The combined organics were washed with saturated sodium hydrogen carbonate (300ml), dried over sodium sulfate, filtered and 30 concentrated *in vacuo*. The residue was distilled under reduced pressure. Bpt 40-45°C at 0.1mmHg. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.92

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(6H, s), 1.10-1.30 (5H, m), 1.30-1.50 (2H, m), 1.66-1.72 (2H, m), 2.26 (1H, m), 2.42 (3H, s).

b) 5-(N-(4,4-Dimethylcyclohexyl)-N-methylamino)-3-oximino-1-methyl-2-oxo-1,4-benzodiazepine

5 Prepared as described in Example 1, steps a) and b) from 1-methyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione and N-methyl-4,4-dimethylcyclohexylamine.

c) N-[3(R,S)-5-(N-(4,4-Dimethylcyclohexyl)-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl]urea

10 The product from step b) (800mg) was dissolved in dry tetrahydrofuran under an atmosphere of nitrogen and ethyl isocyanate (0.37ml) added. The reaction mixture was heated at 60°C for 12h with stirring, then cooled to room temperature and  
15 concentrated in vacuo. The residue was purified by flash column chromatography on silica elution with 1→3% methanol/0.5% 0.88 ammonia solution in dichloromethane. The product was dissolved in methanol (20ml) and palladium on activated charcoal (400mg) was added. The reaction was hydrogenated at  
20 40psi for 2hrs then filtered through a glass fibre filter and concentrated in vacuo without heating. The product was dissolved in dry tetrahydrofuran (2ml) and m-tolylisocyanate (212µl) added. After 20mins diethyl ether (10ml) was added and the product collected by filtration and recrystallised from ethyl  
25 acetate. mp = 172°C (uncorr). <sup>1</sup>H NMR (DMSO) δ 0.82 (3H, s), 0.88 (3H, s), 0.90-1.20 (3H, m), 1.20-1.42 (2H, m), 1.56-2.84 (3H, m), 2.21 (3H, s), 2.69 (3H, s), 3.31 (3H, s), 4.92 (1H, d, J = 8.4Hz), 6.70 (1H, d, J = 8.8Hz), 6.94 (1H, d, J = 8.4Hz), 7.10 (2H, m), 7.17 (1H, s), 7.36 (1H, m), 7.50 (1H, dd, J = 1.3 & 7.7Hz), 7.60  
30 (2H, m), 8.80 (1H, s); MS (CI) m/e 462 [MH]<sup>+</sup>. Anal. Found: C, 69.48; H, 7.69; N, 15.18. C<sub>27</sub>H<sub>35</sub>N<sub>5</sub>O<sub>2</sub> · 0.2H<sub>2</sub>O requires C, 69.71; H, 7.67; N, 15.05%.



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EXAMPLE 78: N-[3(R,S)-5-(N-Cyclohexyl-N-ethylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl] urea

Prepared as for Example 60 using N-ethylcyclohexylamine in place of N-methylcyclohexylamine and recrystallized from ethyl acetate. Mp = 206-207°C. <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 0.83 (3H, m), 0.83-1.9 (10H, m), 2.2 (3H, s), 3.0 (1H, m), 3.3 (4H, m), 4.9 (1H, d, J = 8.9Hz), 6.7 (1H, d, J = 6.5Hz), 6.9-7.6 (8H, Aromatics), 8.8 (1H, s). MS (CI) m/e 448 (MH)<sup>+</sup>. Anal. Found: C, 69.79; H, 7.6; N, 14.82%. C<sub>26</sub>H<sub>33</sub>N<sub>5</sub>O<sub>2</sub> requires C, 70.04; H, 7.49; N, 15.18%.

EXAMPLE 79: N-[3(R,S)-5-(N-Cyclohexyl-N-propylamino)-2,3-dihydro-1-methyl-2-oxo-1H-benzodiazepin-3-yl]-N'-[3-methylphenyl]urea

Prepared as described in Example 60 from 1-methyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-1,5-dione and N-propylcyclohexylamine. Mp = 146°C (uncorr); <sup>1</sup>H NMR (360MHz, DMSO) δ 0.77 (3H, s), 0.86-1.18 (3H, m), 1.20-1.56 (6H, m), 1.56-1.80 (2H, m), 1.88 (1H, m), 2.12 (3H, s), 2.82 (1H, m), 3.31 (3H, s), 3.43 (1H, m), 4.93 (1H, d, J = 8.3Hz), 6.70 (1H, d, J = 6.9Hz), 6.89 (1H, d, J = 8.3Hz), 7.10 (2H, m), 7.18 (1H, s), 7.38 (1H, m), 7.48 (1H, dd, J = 1.3 & 7.9Hz), 7.61 (2H, m), 8.12 (1H, s); MS (CI) m/e 462 [MH]<sup>+</sup>.

EXAMPLE 80: N-[3(R,S)-5-(N-Benzyl-N-cyclohexylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl] urea

a: N-Benzylcyclohexylamine

To a stirred solution of cyclohexylamine (9.34g) in methanol (300ml) was added benzaldehyde (10.0g) followed by activated 3Å molecular sieves. After 1h, sodium cyanoborohydride (7.13g) was added followed by the dropwise

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addition of acetic acid (9.2ml), and the reaction was stirred overnight. The reaction mixture was filtered through hiflo, the solvent removed in vacuo and the resulting white solid was heated under reflux in 5M potassium hydroxide solution for 30 mins. The product was extracted into dichloromethane (3 x 100ml) and the combined organic layers were washed with brine (100ml), dried over sodium sulphate and the solvent was removed in vacuo to give a clear oil. The product was purified by column chromatography (eluting with ethyl acetate) then distillation; bpt = 137°C at 1.0mbarr. <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 0.94-1.24 (5H, m), 1.48-1.88 (5H, m), 2.32 (1H, m), 2.32 (1H, m), 3.10 (2H, s(b)), 3.72 (2H, s), 7.14-7.40 (5H, m).

b) N-[3(R,S)-5-N-Benzyl-N-cyclohexylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl]urea

Prepared as for Example 60 from 1-methyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione and N-benzylcyclohexylamine and recrystallised from ethyl acetate/60-80 petrol. mp = 178-179°C, <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO, VT α 353K) δ 0.92-1.94 (10H, m), 2.21 (3H, s), 3.16 (3H, s), 3.66 (1H, m), 4.22 (1H, d, J = 16Hz), 4.70 (1H, d, J = 16Hz), 4.92 (1H, d, J = 8.3Hz), 6.72 (2H, m), 7.02-7.24 (8H, m), 7.32 (1H, m), 7.44 (1H, m), 7.56 (2H, m), 8.62 (1H, s); MS (CI) m/e = 510 [MH]<sup>+</sup>; Anal. Found: C, 73.08; H, 6.85; N, 13.74. C<sub>31</sub>H<sub>35</sub>N<sub>5</sub>O<sub>2</sub> requires C, 73.06; H, 6.92; N, 13.74%.

EXAMPLE 81: N-[3(R,S)-5-(N-Cyclohexylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl]urea

To a stirred solution of the product of Example 80 (0.50g) in methanol (40ml) under nitrogen was added ammonium formate (0.31g) followed by 10% palladium on carbon (0.50g). The reaction mixture was heated under reflux for 2h then cooled

to room temperature, filtered, washed with methanol (3 x 20ml) and the solvent removed in vacuo. The product was redissolved in dichloromethane (200ml), washed with brine (100ml), dried over sodium sulphate and the solvent removed in vacuo to give a white solid. Recrystallised from ethyl acetate/60-80 petrol. mp = 153-155°C; <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 0.88 (1H, m), 1.06-1.34 (4H, m), 1.88-2.00 (5H, m), 2.22 (3H, s), 3.28 (3H, s), 3.58 (1H, m), 4.88 (1H, d, J = 8.6Hz), 6.54 (1H, d, J = 7.7Hz), 6.68 (1H, d, J = 6.9Hz), 6.86 (1H, d, J = 8.6Hz), 7.08 (2H, m), 7.14 (1H, s), 7.34 (1H, t, J = 7.8Hz), 7.60 (2H, m), 8.77 (1H, s); MS (CI); m/e = 420 [MH]<sup>+</sup>. Anal. Found: C, 65.77; H, 6.97; N, 15.98. C<sub>24</sub>H<sub>29</sub>H<sub>5</sub>O<sub>2</sub>·H<sub>2</sub>O requires C, 65.77; H, 7.14; N, 16.01%.

EXAMPLE 82: N-[3(R,S)-5-(N-Cyclohexyl-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[5-indanyllurea

Prepared as for Example 77c) and Example 69b) using 5-aminoindane. Mp = 232-234°C. <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 1.01-1.98 (16H, m), 2.65 (3H, s), 2.76 (H, m), 4.92 (H, d, J = 8.46Hz), 6.88 (H, d, J = 8.46Hz), 7.23-7.65 (7H, m), 8.65 (H, s). MS (CI) m/z 461 [MH]<sup>+</sup>. Anal Found: C, 68.78; H, 7.34; N, 13.26%. C<sub>27</sub>H<sub>33</sub>N<sub>5</sub>O<sub>2</sub>·0.7EtOAc·0.7H<sub>2</sub>O requires C, 68.48; H, 7.71; N, 13.39%.

EXAMPLE 83: N-[3(R,S)-5-(N-Cyclooctyl-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyllurea

Prepared as for Example 77 using N-methyl cyclooctylamine in place of N-methyl-4,4-dimethylcyclohexylamine. mp = 221-222°C. <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 1.1-1.6 (14H, m), 2.2 (3H, s), 2.66 (3H, s), 3.3 (3H, s), 4.96 (1H, d, J = 1.18Hz), 6.7 (1H, d, J = 6.6Hz), 6.9-7.6 (8H, m), 8.8 (1H, s).

**EXAMPLE 84:** N-[3(R,S)-2,3-Dihydro-5-(2-(N,N-dimethylamino)ethylamino)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl]urea dihydrochloride

5           a) 1,2-Dihydro-5-(2-(N,N-dimethylamino)ethylamino)-1-methyl-3H-1,4-benzodiazepin-2-one

10           A solution of phosphorous pentachloride (8.10g) in anhydrous dichloromethane (350ml) was added dropwise to a stirred suspension of 1-methyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione (6.0g) in anhydrous dichloromethane (150ml). After stirring for 3h the solvent was evaporated, the residue re-dissolved in dichloromethane (200ml), cooled to 4°C and treated dropwise with a solution of

15           N,N-dimethylaminoethylamine (8.81g) in anhydrous dichloromethane (100ml). The cooling bath was removed and the reaction mixture was stirred at room temperature for 2h. The reaction mixture was evaporated to dryness and the residue purified by column chromatography on neutral alumina (Grade 3) using dichloromethane/methanol (30:1) to (20:1) (gradient elution). MS, CI<sup>+</sup>, m/z = 262 for (M+H)<sup>+</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.24 (6H, s), 2.46-2.60 (2H, m), 3.36 (s) and 3.32-3.47 (total 5H, m), 3.61 (1H, d, J = 12Hz), 4.20 (1H, d, J = 12Hz), 5.20 (1H, broad res.), 7.20-7.32 (2H, m), 7.46-7.59 (2H, m).

20

25           b) 1,2-Dihydro-5-(2-(N,N-dimethylamino)ethyl-(t-butyloxycarbonyl)amino)-1-methyl-3H-1,4-benzodiazepin-2-one

30           Di-5-butyldicarbonate (4.33g) was added in portions to a stirred, cooled (4°C) solution of the foregoing benzodiazepine (4.70g) in dichloromethane (40ml). After addition the cooling bath was removed and the reaction mixture stirred at room temperature for 16h. The reaction mixture was evaporated to dryness and the residue purified by column chromatography on neutral alumina (Grade 3) using dichloromethane/methanol (50:1). Mp < 35°C. MS, CI<sup>+</sup>, m/z = 361 for (M+H)<sup>+</sup>. <sup>1</sup>H NMR

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(CDCl<sub>3</sub>) δ 1.22 (9H, s), 2.45 (6H, s), 2.68-2.76 (1H, m), 2.79-2.87 (1H, m), 3.53 (3H, s), 3.72 (1H, d, J = 11Hz), 4.02-4.09 (1H, m), 4.24-4.32 (1H, m), 4.65 (1H, d, J = 11Hz), 7.35 (1H, dd, J<sub>1</sub> = J<sub>2</sub> = 8Hz), 7.41 (1H, d, J = 8Hz), 7.65 (1H, ddd, J<sub>1</sub> = 2Hz, J<sub>2</sub> = J<sub>3</sub> = 8Hz), 7.79 (1H, dd, J<sub>1</sub> = 2Hz, J<sub>2</sub> = 8Hz).

c) 1,2-Dihydro-5-(2-(N,N-dimethylamino)ethyl-(t-butylloxycarbonyl)amino)-1-methyl-3-oximido-3H-1,4-benzodiazepin-2-one

Potassium t-butoxide (3.18g) was added in portions to a stirred, cooled (-20°C) solution of the foregoing benzodiazepine (3.75g) in anhydrous toluene (75ml) under a nitrogen atmosphere. After 15 minutes isopentyl nitrite (1.53ml) was added and the reaction mixture was stirred at -20°C for 1.5h. Powdered carbon dioxide (1.6g) was added in portions and the mixture was stirred for 10 minutes then evaporated to dryness. The residue was purified by column chromatography on neutral alumina (grade 3) using dichloromethane/methanol (30:1) to (10:1) (gradient elution) to afford the oxime (2.50g). mp 105-109°C. <sup>1</sup>H NMR (360MHz, DMSO-d<sub>6</sub>) δ 1.02 (9H, s), 2.18 and 2.20 (6H, each s), 2.41-2.51 (1H, m), 2.82-2.88 (1H, m), 3.29 and 3.32 (3H, each s), 3.93-3.97 (2H, m), 7.29-7.65 (4H, m), 10.10 and 10.97 (1H, each broad s).

d) 3(R,S)-Amino-1,2-dihydro-5-(2-(N,N-dimethylamino)ethyl-(t-butylloxycarbonyl)amino)-1-methyl-3H-1,4-benzodiazepin-2-one

The foregoing oxime (0.50g) was hydrogenated over 5% rhodium on carbon (0.40g) in ethanol (50ml) at 40psi and 60°C for 4h. The reaction mixture was filtered then evaporated to dryness to give the amine (0.462g). R<sub>f</sub> 0.18 in dichloromethane/methanol (5:1) on silica plates. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.07 (9H, s), 1.90-2.30 (2H, broad resonance), 2.29 (6H, s), 2.55-2.70 (2H, m), 3.43 (3H, s), 3.87-3.94 (1H, m), 4.10-4.18 (1H, m), 4.29 (1H, s), 7.19-7.29 (2H, m), 7.48-7.66 (2H, m).

e) N-[3(R,S)-2,3-Dihydro-5-(2-(N,N-dimethylamino)ethyl-(t-butyloxycarbonyl)amino)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl]urea

5 A stirred, cooled (4°C) suspension of the foregoing amine (0.45g) in anhydrous tetrahydrofuran (10ml) was treated with m-tolylisocyanate (0.145ml). The cooling bath was removed and the solution was stirred at room temperature for 30 minutes. The reaction mixture was evaporated to dryness and the residue purified by column chromatography on neutral alumina (grade 10 3) using dichloromethane/methanol (30:1) to afford the title compound which was recrystallised from ethyl acetate/n-hexane (1:5) (0.48g). mp = 112-115°C. MS, CI<sup>+</sup>, m/z = 509 for (M+H)<sup>+</sup>. Anal. Found: C, 63.82; H, 7.07; N, 15.80. C<sub>27</sub>H<sub>36</sub>N<sub>6</sub>O<sub>4</sub> · 0.1C<sub>6</sub>H<sub>14</sub> requires C, 64.09; H, 7.28; N, 16.24%.

15 f) N-[3(R,S)-2,3-Dihydro-5-(2-(N,N-dimethylamino)ethylamino)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl]urea dihydrochloride

A stirred, cooled (4°C) solution of the foregoing benzodiazepine (0.18g) in ethyl acetate (5ml) was treated with 20 ethyl acetate (20ml), pre-saturated with hydrogen chloride gas. The solution was stirred at 4°C for 1h followed by 1h at room temperature, then evaporated to dryness. The product was recrystallised from propan-2-ol/diethyl ether (0.10g). mp 189-192°C. MS, CI<sup>+</sup>, m/z = 409 for (M+H)<sup>+</sup>. <sup>1</sup>H NMR (D<sub>2</sub>O) δ 25 2.30 (3H, s), 2.98 (6H, s), 3.48 (3H, s), 3.53-3.57 (2H, m), 3.79-3.97 (2H, m), 5.56 (1H, s), 7.02 (1H, d, J = 7.5Hz), 7.14-7.16 (2H, m), 7.27 (1H, dd, J<sub>1</sub> = J<sub>2</sub> = 7.5Hz), 7.55 (1H, dd, J<sub>1</sub> = J<sub>2</sub> = 8Hz), 7.62 (1H, d, J = 7.5Hz), 7.86-7.91 (2H, m). Anal. Found: 30 C, 53.89; H, 6.38; N, 16.89. C<sub>22</sub>H<sub>28</sub>N<sub>6</sub>O<sub>2</sub> · 2HCl · 0.6H<sub>2</sub>O requires C, 53.68; H, 6.39; N, 17.07%.

EXAMPLE 85: N-[3(R,S)-2,3-Dihydro-5-(N-(2-N-morpholinoethyl)-N-methylamino)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl]urea

Prepared in the same way as Example 77 except using  
5 N-methyl-(2-aminoethyl)morpholine. Mp = 174°C (uncorr); <sup>1</sup>H  
NMR (DMSO) δ 2.10-2.38 (9H, m), 2.43 (1H, m), 2.82 (3H, s),  
3.12 (1H, m), 3.32 (3H, s), 3.48 (4H, m), 4.92 (1H, d, J = 8.4Hz),  
6.70 (1H, d, J = 7.1Hz), 6.96 (1H, d, J = 8.4Hz), 7.08 (2H, m),  
7.17 (1H, s), 7.37 (1H, m), 7.57 (2H, m), 7.63 (1H, m), 8.81 (1H,  
10 s); MS (CI) m/e 465 [MH]<sup>+</sup>. Anal. Found: C, 64.54; H, 6.66; N,  
18.04. C<sub>25</sub>H<sub>32</sub>N<sub>6</sub>O<sub>3</sub> requires. C, 64.64; H, 6.94; N, 18.09%.

EXAMPLE 86: N-[3(R,S)-5-(N-Cycloheptyl)-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-(5-methylpyridine)] urea

a) 5-(N-Cycloheptyl-N-methylamino)-1-methyl-2-oxo-1,4-benzodiazepine

Prepared analogously to Example 1a) from 1-methyl-  
1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione and N-methyl  
20 cycloheptylamine. <sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ 1.0-1.90 (12H,  
m), 1.96 (1H, m), 2.78 (3H, s), 3.36 (3H, s), 3.48 (1H, d,  
J=12.2Hz), 4.23 (1H, d, J=12.2Hz), 7.24 (2H, m), 7.48 (2H, m).

b) 5-(N-cycloheptyl-N-methylamino)-1-methyl-3-oximino-2-oxo-1,4-benzodiazepine

25 Prepared analogously to Example 1b).

c) N-[3(R,S)-5-(N-Cycloheptyl)-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-(5-methylpyridine)] urea

To the product of part b) (1.9g) in acetic acid (50ml) was  
30 added trifluoroacetic acid (4.5ml) and zinc (3.8g) and the  
reaction mixture was heated to 40°C with rapid stirring for 2hrs.  
The reaction mixture was cooled to room temperature, filtered

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through hyflo, evaporated and azeotroped with toluene. The residue was dissolved in dry tetrahydrofuran (10ml) and added to a solution of 3-amino-5-methyl pyridine (0.63g), triphosgene (0.57g) and triethylamine (2.2ml) in dry tetrahydrofuran (30ml) and the reaction was allowed to stir at room temperature for 17hrs. The reaction mixture was concentrated in vacuo and the residue purified by flash column chromatography elution with 0→5% MeOH/0.5% 0.88 ammonia solution/dichloromethane followed by purification on HPLC elution with 0→5% MeOH/0.5% 0.88 ammonia solution/dichloromethane. Product recrystallised from ethyl acetate. mpt = 235°C (uncorr). <sup>1</sup>H NMR DMSO δ 1.18 (1H, m), 1.40 (6H, m), 1.90 (1H, m), 2.21 (3H, s), 2.63 (3H, s), 3.32 (3H, s), 4.93 (1H, d, J=8.3Hz), 7.07 (1H, d, J=8.3Hz), 7.37 (1H, m), 7.50 (1H, dd, J=1.4 and 7.8Hz), 7.61 (3H, m), 7.96 (1H, s), 8.29 (1H, d, J=2.2Hz), 9.02 (1H, s). MS (CI) m/e 449 [MH]<sup>+</sup>. Anal. Found C, 66.67; H, 7.19; N, 18.63. C<sub>25</sub>H<sub>32</sub>N<sub>6</sub>O<sub>2</sub> requires C, 66.94; H, 7.19; N, 18.74%.

EXAMPLE 87: 3(R,S)-N-(5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide

a) 5-(3-Azabicyclo[3.2.2]nonan-3-yl)-1,2-dihydro-3H-1-methyl-3-(O-(ethylaminocarbonyl)oximido)-1,4-benzodiazepin-2-one

The product of Example 31a) (17.5g), ethyl isocyanate (7.3ml) and triethylamine (4.6ml) were heated at 65°C, with stirring, in anhydrous tetrahydrofuran (900ml) for 4 hours. The solvent was evaporated and the residue was purified by column chromatography on silica using dichloromethane → 2% methanol/dichloromethane (gradient). (20.8g). mp 168°C.

b) 3(R,S)-Amino-5-(3-azabicyclo[3.2.2]nonan-3-yl)-1,2-dihydro-3H-1-methyl-1,4-benzodiazepin-2-one



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The foregoing oxime derivative (11.0g) was hydrogenated in methanol (1L) over 10% palladium on carbon (4.5g) at 45 psi and ambient temperature for 3 hours. The mixture was filtered and the solvent was evaporated to give the amine as a foam (8.0g). mp 160-163°C (ethyl acetate). Found: C, 68.82; H, 7.67; N, 17.69.  $C_{18}H_{24}N_4O$  requires C, 69.20; H, 7.74; N, 17.93%.

c) 3(R,S)-N-(5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide

A solution of the foregoing amine (1.50g) in dimethylformamide (10ml) was treated with indole-2-carboxylic acid (852mg), 1-hydroxybenzotriazole (714mg), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (1.01g) and triethylamine (1.4ml). After stirring for 18 hours at room temperature the solid obtained was collected then triturated with methanol to afford the title compound (1.60g). mp 210-214°C (chloroform/diethyl ether). MS,  $CI^+$ ,  $m/z = 456$  for  $(M+H)^+$ .  $^1H$  NMR (360MHz,  $CDCl_3$ )  $\delta$  1.44-1.95 (8H, m), 1.95-2.08 (2H, m), 3.26-3.42 (2H, m), 3.44 (3H, s), 3.56-3.70 (2H, m), 5.46 (1H, d,  $J = 8Hz$ ), 7.06-7.74 (10H, m), 9.22 (1H, broad resonance). Found: C, 69.11; H, 6.34; N, 14.74.  $C_{27}H_{29}N_5O_2 \cdot 0.66H_2O$  requires C, 69.36; H, 6.54; N, 14.98%.

EXAMPLE 88: (-)-N-(5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide hydrochloride

The racemic compound (Example 87, 1.60g) was separated into its enantiomers using preparative chiral HPLC on a Pirkle dinitrobenzoyleucine column (5 $\mu$ ) [(250 x 21.4)mm] eluting with 2% methanol in 1-chlorobutane (including 1% acetic acid). Flow rate 20ml/minute, U.V. detection at 305nm. Analysis was performed on an analytical Pirkle dinitrobenzoyleucine column

(5 $\mu$ ) [(250 x 4.6)mm] eluting with 5% methanol in 1-chlorobutane (including 1% acetic acid). Flow rate 1.5ml/minute, U.V. detection at 250nm.

5 The free base was liberated and obtained as a colourless solid (780mg). The hydrochloride salt had mp 280-282°C (chloroform). MS,  $\text{Cl}^+$ ,  $m/z = 456$  for  $(\text{M}+\text{H})^+$ .  $[\alpha]^{23^\circ}_{\text{D}} = -253^\circ$  ( $c=0.2$ , methanol). HPLC: > 99% ee. Found: C, 65.86; H, 6.15; N, 14.44; Cl, 6.87.  $\text{C}_{27}\text{H}_{29}\text{N}_5\text{O}_2\cdot\text{HCl}$  requires C, 65.91; H, 6.14; N, 14.23; Cl, 7.20%.

10

EXAMPLE 89: (+)-N-(5-(3-Azabicyclo[3.2.2]nonan-3-yl)-2,3-ihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide dihydrochloride

15 The title compound was obtained (800mg) using the procedure described in Example 88. The dihydrochloride salt had mp 279-280°C (chloroform). MS,  $\text{Cl}^+$ ,  $m/z = 456$  for  $(\text{M}+\text{H})^+$ .  $[\alpha]^{23^\circ}_{\text{D}} = +222^\circ$  ( $c=0.2$ , methanol). HPLC: 93% ee. Found: C, 59.73; H, 5.60; N, 12.55; Cl, 15.34.  $\text{C}_{27}\text{H}_{29}\text{N}_5\text{O}_2\cdot 2.4\text{HCl}$  requires C, 59.72; H, 5.83; N, 12.90; Cl, 15.67%.

20

EXAMPLE 90: 3(R,S)-N-(2,3-Dihydro-5-(homopiperidin-1-yl)-1-(2-methylpropyl)-2-oxo-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide

25 a) 1,2-Dihydro-3H-5-(homopiperidin-1-yl)-1-(2-methylpropyl)-1,4-benzodiazepin-2-one

The title compound was prepared from 1-(2-methylpropyl)-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione, phosphorus pentachloride and homopiperidine. mp > 210°C (dec.). Found: C, 71.88; H, 8.70; N, 12.95.  $\text{C}_{19}\text{H}_{27}\text{N}_3\text{O}\cdot 0.25\text{H}_2\text{O}$  requires C, 71.78; H, 8.72; N, 13.22%.

30

b) 1,2-Dihydro-3H-5-(homopiperidin-1-yl)-1-(2-methylpropyl)-3-oximido-1,4-benzodiazepin-2-one

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The title compound was prepared from the foregoing benzodiazepine, potassium t-butoxide and isopentyl nitrite in toluene.

5 c) 3(R,S)-Amino-1,2-dihydro-3H-5-(homopiperidin-1-yl)-1-(2-methylpropyl)-1,4-benzodiazepin-2-one

The title compound was prepared from the foregoing oxime using previously described procedures.

10 d) 3(R,S)-N-(2,3-Dihydro-5-(homopiperidin-1-yl)-1-(2-methylpropyl)-2-oxo-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide

15 The title compound was obtained from the foregoing amine, indole-2-carboxylic acid, 1-hydroxybenzotriazole, 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride and triethylamine in dimethylformamide. mp > 264°C. Found: C, 71.47; H, 7.02; N, 15.14. C<sub>28</sub>H<sub>33</sub>N<sub>5</sub>O<sub>2</sub> requires C, 71.31; H, 7.05; N, 14.85%.

20 EXAMPLE 91: (-)-N-(2,3-Dihydro-5-(homopiperidin-1-yl)-1-(2-methylpropyl)-2-oxo-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide

25 The racemate of Example 90 was separated into its enantiomers using a semi-preparative dinitrobenzoylleucine Pirkle column (5μ) [(250 x 20)mm] eluting with 3% methanol in 1-chlorobutane (including 1% acetic acid). The free base was liberated and obtained as a colourless solid. mp 243-246°C. [α]<sup>23°C</sup><sub>D</sub> = -17° (c=0.2, methanol). Found: C, 71.56; H, 6.97; N, 14.80. C<sub>28</sub>H<sub>33</sub>N<sub>5</sub>O<sub>2</sub> requires C, 71.31; H, 7.05; N, 14.85%.

30 EXAMPLE 92: (+)-N-(2,3-Dihydro-5-(homopiperidin-1-yl)-1-(2-methylpropyl)-2-oxo-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide

Obtained as for Example 91. mp 240-241°C.  $[\alpha]^{23}_{\text{D}} = +15^{\circ}$  (c=0.2, methanol). Found: C, 65.91; H, 6.77; N, 13.36.  $\text{C}_{28}\text{H}_{33}\text{N}_5\text{O}_2 \cdot 2\text{H}_2\text{O}$  requires C, 66.25; H, 7.35; N, 13.80%.

5     EXAMPLE 93: 3(R,S)-N-(2,3-Dihydro-5-(homopiperidin-1-yl)-1-(2-methylpropyl)-2-oxo-1H-1,4-benzodiazepin-3-yl)-(2S)-indoline-2-carboxamide

10     Prepared analogously to Example 87 from 3(R,S)-amino-1,2-dihydro-3H-5-(homopiperidin-1-yl)-1-(2-methylpropyl)-1,4-benzodiazepin-2-one and (S)-(-)-indoline-2-carboxylic acid. mp 105-106°C. Found: C, 70.26; H, 7.24; N, 14.14.  $\text{C}_{28}\text{H}_{35}\text{N}_5\text{O}_2 \cdot 0.4\text{H}_2\text{O}$  requires C, 69.94; H, 7.51; N, 14.57%.

15     EXAMPLE 94: 3(R,S)-N-(2,3-Dihydro-5-(homopiperidin-1-yl)-1-(2-methylpropyl)-2-oxo-1H-1,4-benzodiazepin-3-yl)-1H-indole-3-acetamide

20     Prepared analogously to Example 87 from 3(R,S)-amino-1,2-dihydro-3H-5-(homopiperidin-1-yl)-1-(2-methylpropyl)-1,4-benzodiazepin-2-one and indole-3-acetic acid. mp 178-180°C. Found: C, 72.11; H, 7.10; N, 14.45.  $\text{C}_{29}\text{H}_{35}\text{N}_5\text{O}_2$  requires C, 71.72; H, 7.26; N, 14.42%.

25     EXAMPLE 95: 3(R,S)-N-(2,3-Dihydro-5-(4-methylpiperidin-1-yl)-1-(2-methylpropyl)-2-oxo-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide

30     a)     1,2-Dihydro-3H-5-(4-methylpiperidin-1-yl)-1-(2-methylpropyl)-1,4-benzodiazepin-2-one

Prepared from 1-(2-methylpropyl)-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione, phosphorus pentachloride and 4-methylpiperidine. Rf 0.76 in dichloromethane/methanol (9:1) on silica plates. MS,  $\text{CI}^+$ ,  $m/z = 314$   $[\text{M}+\text{H}]^+$ .

b)     1,2-Dihydro-3H-5-(4-methylpiperidin-1-yl)-3-oximido-1,4-benzodiazepin-2-one

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Prepared from the foregoing benzodiazepine, potassium t-butoxide and isopentyl nitrite in toluene. mp 188-191°C (ethyl acetate/n-hexane). MS, CI<sup>+</sup>, m/z = 343 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 0.81-1.10 and 1.20-2.00 (14H, each m), 2.80-3.00 (1H, m), 3.10-3.35 (1H, m), 3.34 (1H, dd, J<sub>1</sub> = 6Hz, J<sub>2</sub> = 14Hz), 3.60-3.90 (2H, m), 4.34 (1H, dd, J<sub>1</sub> = 9Hz, J<sub>2</sub> = 14Hz), 4.44-5.00 (1H, m), 7.12-7.48 (4H, m).

c) 1,2-Dihydro-3-(O-(ethylaminocarbonyl)-oximido)-3H-5-(4-methylpiperidin-1-yl)-1-(2-methylpropyl)-1,4-benzodiazepin-2-one

The foregoing oxime (800mg) was treated with triethylamine (0.2ml) and ethyl isocyanate (0.37ml) in anhydrous tetrahydrofuran (80ml) then heated at reflux for 4 hours. The reaction mixture was cooled, evaporated to dryness to give a cream foam (960mg). mp 75-79°C. MS, CI<sup>+</sup>, m/z 414 for [M+H]<sup>+</sup>.

d) 3(R,S)-Amino-1,2-dihydro-3H-5-(4-methylpiperidin-1-yl)-1-(2-methylpropyl)-1,4-benzodiazepin-2-one

The foregoing carbamate-oxime (960mg) was hydrogenated at 45 psi over 10% palladium on charcoal (960mg) in ethyl acetate (120ml) for 5 hours. The reaction mixture was filtered, then evaporated to dryness to give the amine (725mg). Rf 0.28 in dichloromethane/methanol (9:1) on silica plates.

e) 3(R,S)-N-(2,3-Dihydro-5-(4-methylpiperidin-1-yl)-1-(2-methylpropyl)-2-oxo-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide

A stirred solution of the foregoing amine (725mg) in dimethylformamide (10ml) was treated with 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (497mg), 1-hydroxybenzotriazole (35mg), indole-2-carboxylic acid (419mg) then finally triethylamine (0.72ml). The reaction mixture was stirred at ambient temperature for 18 hours, treated with water (30ml), and the resulting solid collected by

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filtration. The solid was purified through a short silica column using dichloromethane/methanol (20:1) then recrystallised from ethyl acetate/n-hexane (455mg). mp 248-249°C. MS, CI<sup>+</sup>, m/z = 472 [M+H]<sup>+</sup>. Found: C, 71.79; H, 7.01; N, 14.58. C<sub>28</sub>H<sub>33</sub>N<sub>5</sub>O<sub>2</sub> requires C, 71.31; H, 7.05; N, 14.85%.

EXAMPLE 96: N-[3(R,S)-2,3-Dihydro-1-methyl-5-(4-methylpiperidin-1-yl)-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[3-(N-methyl-N'-piperazinyl)phenyl]urea

10 a) 1,2-Dihydro-1-methyl-5-(4-methylpiperidin-1-yl)-3-O-ethylaminocarbonyloximido-3H-1,4-benzodiazepin-2-one

Prepared analogously to Example 17e from 1,2-dihydro-1-methyl-5-(4-methylpiperidin-1-yl)-3-oximido-3H-1,4-benzodiazepin-2-one (Example 7b, 0.5g). <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.00 (3H, brs), 1.13 (3H, t, J = 7.2Hz), 1.22-1.42 (2H, m), 1.54-1.90 (3H, m), 2.78-3.30 (4H, m), 3.44 (3H, s), 3.56-3.78 (1H, m), 4.54-4.86 (1H, m), 6.37-6.45 (1H, m), 7.21-7.38 (3H, m), 7.46-7.54 (1H, m).

b) 3-(N-Methyl-N'-piperazinyl)-1-nitrobenzene

20 A mixture of N-methylbis (2-chloroethyl)amine hydrochloride (9.8g) and 3-nitroaniline (7.0g) in 1-butanol (100ml) was heated at reflux for 60h then cooled to room temperature. Sodium carbonate (2.8g) was then added and the mixture heated at reflux for a further 18h, then cooled to 0°C and filtered. The solid was collected, washed with anhydrous ether then partitioned between dichloromethane (200ml) and sodium hydroxide solution (1M, 150ml). The organic layer was separated and the aqueous phase washed once more with dichloromethane (200ml). The combined organic layers were dried (K<sub>2</sub>CO<sub>3</sub>) and evaporated *in vacuo*. The resultant residue was chromatographed on silica gel, using dichloromethane:methanol (96:4) as the eluant, to afford an

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orange oil. The oil crystallised on standing and the resultant solid was triturated with petrol (60/80) to give the desired piperazine (5.64g). <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 2.37 (3H, s), 2.58 (4H, t, J = 5Hz), 3.30 (4H, t, J = 5Hz), 7.18 (1H, dd, J = 9 and 3Hz), 7.35 (1H, t, J = 8Hz), 7.64 (1H, dd, J = 9 and 2Hz), 7.71 (1H, d, J = 2Hz). MS (CI, NH<sub>3</sub>) 222 (M+1).

c) 1-Amino-3-(N-methyl-N'-piperazinyl)benzene

A solution of 3-(N-methyl-N'-piperazinyl)-1-nitrobenzene (1.17g) in ethanol (40ml) was hydrogenated at 25 psi for 20 min in the presence of a palladium on carbon catalyst (200mg, 17% (w/w)). The catalyst was filtered off and the solvent evaporated *in vacuo*. The residue was chromatographed on silica gel, using a gradient elution of petrol:ether (1:1) followed by dichloromethane:methanol (95:5) to give a colourless oil, which was azeotroped with toluene (20ml) then left at 0°C overnight. After this time the oil had crystallized, and after trituration with petrol (60/80) the desired aniline (0.86g) was isolated as a white solid. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 2.34 (3H, s), 2.55 (4H, t, J = 5Hz), 3.18 (4H, t, J = 5Hz), 3.60 (2H, brs), 6.20 (1H, dd, J = 8 and 2Hz), 6.25 (1H, t, J = 2Hz), 6.36 (1H, dd, J = 8 and 2Hz), 7.04 (1H, t, J = 8Hz). MS (CI, NH<sub>3</sub>) 192 (M+1).

d) N-[3(R,S)-2,3-Dihydro-1-methyl-5-(4-methylpiperidin-1-yl)-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-(N-methyl-N'-piperazinyl)phenyl] urea

To a solution of the product of part a) (0.62g) in methanol (30ml) was added 10% palladium on carbon (0.2g, 32% (w/w)). The mixture was hydrogenated at 40 psi for 2h. Further 10% palladium on carbon (0.1g, 16% (w/w)) was added and the mixture hydrogenated at 40 psi for another 1h. The catalyst was then filtered off and washed with methanol. The solvent was evaporated *in vacuo* to give the amine (0.48g).

To a solution of 1-amino-3-(N-methyl-N'-piperazinyl)benzene (0.48g) in anhydrous tetrahydrofuran (30ml) cooled to

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0°C under an atmosphere of nitrogen was added triphosgene (0.25g). Triethylamine (1.0ml) was added dropwise. After stirring at 0°C for 30 min a solution of the amine (0.48g) in anhydrous tetrahydrofuran (10ml) was added dropwise. The mixture was stirred at 0°C for 5 min and then allowed to warm to ambient temperature and stirred for 10 min. The solvent was evaporated *in vacuo* and the residue partitioned between ethyl acetate (50ml) and water (50ml). The undissolved solid was collected by filtration and purified by chromatography on silica gel using 95:5:1, dichloromethane:methanol:aqueous ammonia solution increasing the ratio to 90:10:1, to give the title compound (0.55g). Mp 160°C (dec.). <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 0.95 (3H, d, J = 6.2Hz), 1.05-1.21 (1H, m), 1.28-1.37 (1H, m), 1.46-1.62 (2H, m), 1.64-1.74 (1H, m), 2.45 (3H, s), 2.57-2.80 (6H, m), 3.25-3.35 (4H, m), 3.41 (3H, s), 3.47-3.60 (1H, m), 3.86-3.96 (1H, m), 5.26 (1H, d, J = 7.8Hz), 6.52-6.58 (2H, m), 6.65 (1H, d, J = 7.9Hz), 6.98 (1H, brs), 7.11 (1H, t, J = 8.1Hz), 7.16-7.20 (1H, m), 7.21-7.33 (2H, m), 7.47-7.55 (2H, m).



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EXAMPLE 97A Tablets containing 1-25mg of compound

		<u>Amount mg</u>		
	Compound of formula (I)	1.0	2.0	25.0
5	Microcrystalline cellulose	20.0	20.0	20.0
	Modified food corn starch	20.0	20.0	20.0
	Lactose	58.5	57.5	34.5
	Magnesium Stearate	0.5	0.5	0.5

10 EXAMPLE 97B Tablets containing 26-100mg of compound

		<u>Amount mg</u>		
	Compound of formula (I)	26.0	50.0	100.0
	Microcrystalline cellulose	80.0	80.0	80.0
	Modified food corn starch	80.0	80.0	80.0
15	Lactose	213.5	189.5	139.5
	Magnesium Stearate	0.5	0.5	0.5
20	The compound of formula (I), cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active compound per tablet.			

25

EXAMPLE 98 Parenteral injection

		<u>Amount mg</u>
	Compound of formula (I)	1 to 100
	Citric Acid Monohydrate	0.75
30	Sodium Phosphate	4.5
	Sodium Chloride	9
	Water for Injections	to 1ml
	The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The	

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compound of formula (I) is dissolved or suspended in the solution and made up to volume.

EXAMPLE 99 Topical formulation

5		<u>Amount mg</u>
	Compound of formula (I)	1-10
	Emulsifying Wax	30
	Liquid paraffin	20
	White Soft Paraffin	to 100

10 The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The compound of formula (I) is added and stirring continued until dispersed. The mixture is then cooled until solid.

15

BIOLOGICAL ACTIVITY

The CCK-A and CCK-B antagonising activity of the compounds described herein was evaluated using the assays described in published European patent application no. 0514133. The method essentially involves determining the concentration of the test compound required to displace 50% of the specific  $^{125}\text{I}$ -CCK from rat pancreas (CCK-A) or guinea pig brain (CCK-B). The data in Table 1 were obtained for compounds of the Examples.

30

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TABLE I  
CCK RECEPTOR BINDING RESULTS  
IC<sub>50</sub>(nM)

	Compound of Ex #	<sup>125</sup> I-CCK <u>Pancreas</u>	<sup>125</sup> I-CCK <u>Brain</u>
5	1	724	14.8
	2	871	2.02
	3	544	11.6
10	4	35	1.19
	5 (enantiomer A)	738	0.49
	5 (enantiomer B)	7.8	14.8
	6	235	10.9
15	7	7.74	1.64
	8 (enantiomer A)	981	0.35
	8 (enantiomer B)	2.61	23.2
	9	8.97	0.21
	10 (enantiomer A)	421	0.76
	10 (enantiomer B)	0.42	12.6
20	11	25.2	4.22
	12	2180	0.28
	13	496	1.53
	14 (enantiomer A)	3220	11.6
	14 (enantiomer B)	11.4	174
25	15 (enantiomer A)	1902	3.47
	15 (enantiomer B)	163	75
	16	2650	19.1
	17	27.2	0.2
	18 (enantiomer A)	765	0.64
30	20 (enantiomer A)	3294	1.52
	20 (enantiomer B)	40	44
	22 (enantiomer A)	3670	32.9
	24 (enantiomer A)	2250	0.927
	24 (enantiomer B)	46	50

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	26	>3000	0.27
	27	15	33
	28 (enantiomer A)	239	27.8
	28 (enantiomer B)	3.97	281
5	30	347	0.36
	31	20	0.53
	32	>3000	22
	33	1604	0.10
	34	6.46	26.7
10	35	39.6	0.82
	36	1400	0.32
	37	9	144
	38	7.93	0.71
	39	4010	0.17
15	40	8.8	36.3
	41	>3000	0.37
	42	80.4	1.79
	43	>3000	48.3
	44	70.2	0.52
20	45	>3000	0.42
	46	23.7	20.1
	47	26.6	1.01
	48	2418	1.11
	49	9.65	82.7
25	50	10	3.9
	51	28.5	5.49
	52	18.5	0.25
	53	3760	0.18
	54	8.4	68
30	55	>3000	0.73
	56	62	47
	57	12.3	4.6
	58	2260	2.0
	59	9.7	144

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	60	186	2.56
	61	704	0.22
	62	114	35.2
	63	304	1.36
5	64	2065	0.22
	65	138	13.7
	66	83.6	0.79
	67	1999	0.10
	68	53.4	26.6
10	69	469	2.82
	70	>3000	0.61
	71	145	86
	72	176	10.3
	73	>3000	1410
15	74	192	7.3
	75	314	46.9
	76	760	3.12
	77	135	81.1
	78	891	4.5
20	79	1700	13.4
	80	1135	32.4
	81	14.9	23.2
	82	815	0.47
	83	283	3.67
25	84	>3000	1900
	85	>3000	785
	86	831	31.3
	87	0.87	509
	88	393	66
30	89	0.26	653
	90	8.7	225
	93	101	348
	94	646	119
	95	11.6	161

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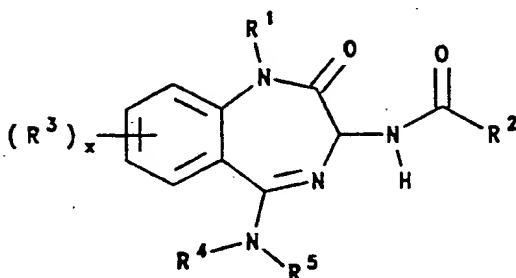
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## CLAIMS:

1. A compound of formula (I), or a salt or  
5 prodrug thereof:



(I)

wherein:

- $R^1$  represents H,  $C_{1-6}$ alkyl optionally substituted by one or more halo,  $C_{3-7}$ cycloalkyl, cyclopropylmethyl,  $(CH_2)_r$ imidazolyl,  $(CH_2)_r$ triazolyl,  $(CH_2)_r$ tetrazolyl (where  $r$  is 1, 2 or 3),  $CH_2CO_2R^{11}$  (where  $R^{11}$  is  $C_{1-4}$ alkyl) or  $CH_2CONR^6R^7$  (where  $R^6$  and  $R^7$  each independently represents H or  $C_{1-4}$ alkyl, or  $R^6$  and  $R^7$  together form a chain  $(CH_2)_p$  where  $p$  is 4 or 5);

- $R^2$  represents  $NHR^{12}$  or  $(CH_2)_sR^{13}$  where  $s$  is 0, 1 or 2;

- $R^3$  represents  $C_{1-6}$ alkyl, halo or  $NR^6R^7$ , where  $R^6$  and  $R^7$  are as previously defined;

- $R^4$  and  $R^5$  each independently represents H,  $C_{1-12}$ alkyl optionally substituted by  $NR^9R^{9'}$  (where  $R^9$  and  $R^{9'}$  are as previously defined) or an azacyclic or azabicyclic group,  $C_{4-9}$ cycloalkyl optionally substituted by one or more  $C_{1-4}$ alkyl groups,  $C_{4-9}$ cycloalkyl $C_{1-4}$ alkyl optionally substituted in the cycloalkyl ring by one or more  $C_{1-4}$ alkyl groups, optionally substituted aryl,

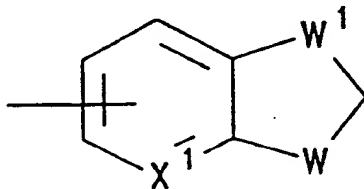
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optionally substituted arylC<sub>1-6</sub>alkyl or azacyclic or azabicyclic groups, or R<sup>4</sup> and R<sup>5</sup> together form the residue of an optionally substituted azacyclic or azabicyclic ring system;

5                   x is 0, 1, 2 or 3;

                  R<sup>12</sup> represents a phenyl or pyridyl group optionally substituted by one or more substituents selected from C<sub>1-6</sub>alkyl, halo, hydroxy, C<sub>1-4</sub>alkoxy, (CH<sub>2</sub>)<sub>q</sub>-tetrazolyl optionally substituted in the tetrazole  
10 ring by C<sub>1-4</sub>alkyl, (CH<sub>2</sub>)<sub>q</sub>-imidazolyl, (CH<sub>2</sub>)<sub>q</sub>-triazolyl (where q is 0, 1, 2 or 3), 5-hydroxy-4-pyrone, NR<sup>6</sup>R<sup>7</sup>, NR<sup>9</sup>COR<sup>11</sup>, NR<sup>9</sup>CONR<sup>9'</sup>R<sup>11</sup> (where R<sup>9</sup> and R<sup>9'</sup> are each independently H or C<sub>1-4</sub>alkyl and R<sup>11</sup> is as previously defined), CONR<sup>6</sup>R<sup>7</sup> (where R<sup>6</sup> and R<sup>7</sup> are as previously  
15 defined), SO(C<sub>1-6</sub>alkyl), SO<sub>2</sub>(C<sub>1-6</sub>alkyl), trifluoromethyl, CONHSO<sub>2</sub>R<sup>8</sup>, SO<sub>2</sub>NHCOR<sup>8</sup> (where R<sup>8</sup> is C<sub>1-6</sub>alkyl, optionally substituted aryl, 2,2-difluorocyclopropane or trifluoromethyl), SO<sub>2</sub>NHR<sup>10</sup> (where R<sup>10</sup> is a nitrogen containing heterocycle), B(OH)<sub>2</sub>, (CH<sub>2</sub>)<sub>q</sub>CO<sub>2</sub>H, where q is  
20 as previously defined; or

                  R<sup>12</sup> represents a group

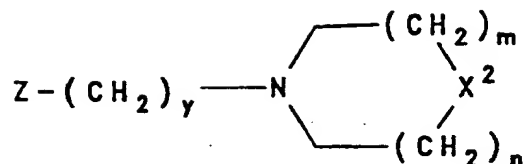


where X<sup>1</sup> represents CH or N; W represents CH<sub>2</sub> or NR<sup>9</sup>, where R<sup>9</sup> is as previously defined, and W<sup>1</sup> represents CH<sub>2</sub>, or W and W<sup>1</sup> each represent O; or

30                   R<sup>12</sup> represents phenyl substituted by a group

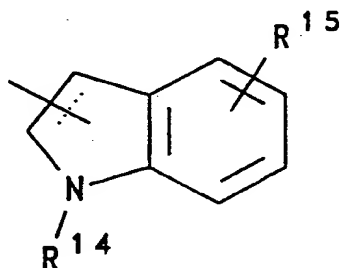


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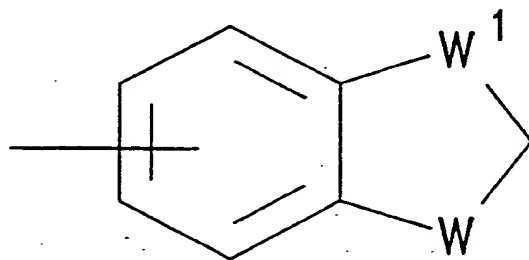
wherein  $X^2$  is O, S or  $NR^9$ , where  $R^9$  is as previously defined; Z is a bond, O or S; m is 1, 2 or 3; n is 1, 2 or 3; and y is 0, 1, 2 or 3;

$R^{13}$  represents a group



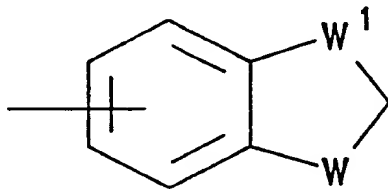
wherein  $R^{14}$  represents H or  $C_{1-6}$ alkyl;  $R^{15}$  represents H,  $C_{1-6}$ alkyl, halo or  $NR^6R^7$ , where  $R^6$  and  $R^7$  are a previously defined; and the dotted line represents an optional covalent bond;

with the proviso that, when  $NR^4R^5$  represents an unsubstituted azacyclic ring system,  $R^2$  does not represent  $NHR^{12}$  where  $R^{12}$  is optionally substituted phenyl or

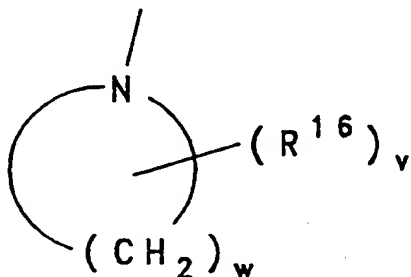


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2. A compound as claimed in claim 1 wherein  $R^1$  represents  $C_{1-6}$ alkyl,  $C_{3-7}$ cycloalkyl, cyclopropylmethyl,  $CH_2CO_2R^{11}$  or  $CH_2CONR^6R^7$ ;  $R^2$  represents  $NHR^{12}$  where  $R^{12}$  represents a phenyl group optionally substituted by one or more substituents selected from  $C_{1-6}$ alkyl, halo, hydroxy,  $C_{1-4}$ alkoxy,  $(CH_2)_q$ -tetrazolyl optionally substituted in the tetrazole ring by  $C_{1-4}$ alkyl,  $(CH_2)_q$ -imidazolyl,  $(CH_2)_q$ -triazolyl, 5-hydroxy-4-pyrone,  $NR^6R^7$ ,  $NR^9COR^{11}$ ,  $NR^9CONR^9R^{11}$ ,  $CONR^6R^7$ ,  $SO(C_{1-6}alkyl)$ ,  $SO_2(C_{1-6}alkyl)$ , trifluoromethyl,  $CONHSO_2R^8$ ,  $SO_2NHCOR^8$ ,  $SO_2NHR^{10}$ ,  $B(OH)_2$  and  $(CH_2)_tCO_2H$ , where  $t$  is zero, 1 or 2; or  $R^{12}$  represents a group

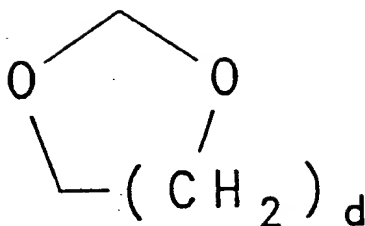


and  $NR^4R^5$  represents a group



wherein each  $R^{16}$  independently represents  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy, hydroxy, oxo,  $SR^{11}$ ,  $NR^6R^7$ ,  $NR^9C_{1-4}alkylR^{17}$ ,  $=NOR^9$  or

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where  $R^{11}$ ,  $R^6$ ,  $R^7$  and  $R^9$  are as previously defined,  $R^{17}$  is halo or trifluoromethyl, and  $d$  is 2 or 3;  $v$  is 1, 2, 3, 4, 5, 6, 7 or 8; and  $w$  is 4, 5, 6, 7, 8, 9, 10 or 11.

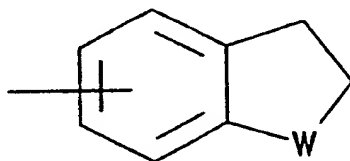
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3. A compound as claimed in claim 2 wherein  $R^{12}$  represents a phenyl group optionally substituted by one or more substituents selected from  $C_{1-6}$ alkyl, halo, hydroxy,  $C_{1-4}$ alkoxy,  $(CH_2)_q$ -tetrazolyl optionally substituted in the tetrazole ring by  $C_{1-4}$ alkyl,  $(CH_2)_q$ -imidazolyl,  $(CH_2)_q$ -triazolyl, 5-hydroxy-4-pyrone,  $NR^6R^7$ ,  $NR^9COR^{11}$ ,  $NR^9COR^9R^{11}$ ,  $CONR^6R^7$ ,  $SO(C_{1-6}alkyl)$ ,  $SO_2(C_{1-6}alkyl)$ , trifluoromethyl,  $CONHSO_2R^8$ ,  $SO_2NHCOR^8$ ,  $SO_2NHR^{10}$ ,  $B(OH)_2$  and  $(CH_2)_tCO_2H$ ; or

15

20

$R^{12}$  represents a group



where  $W$  represents  $CH_2$  or  $NR^9$ ;

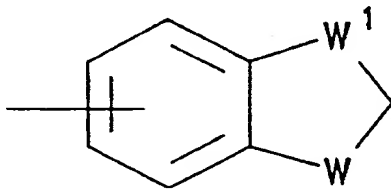
$R^{16}$  represents  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy, hydroxy, oxo,  $SR^{11}$ ,  $NR^6R^7$ ,  $NR^9C_{1-4}alkylR^{17}$ ,  $=NOR^9$  or  $OR^{18}$  or  $OR^{19}$ ,

30

where  $R^{18}$  and  $R^{19}$  each independently represent  $C_{1-4}$ alkyl or  $R^{18}$  and  $R^{19}$  together form a chain  $CH_2CH_2$  or  $CH_2CH_2CH_2$ ; and  $v$  is 1.

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4. A compound as claimed in claim 1 wherein  $R^1$  represents H,  $C_{1-6}$ alkyl,  $C_{3-7}$ cycloalkyl, cyclopropylmethyl,  $(CH_2)_r$ imidazolyl,  $(CH_2)_r$ triazolyl,  $(CH_2)_r$ tetrazolyl,  $CH_2CO_2R^{11}$  or  $CH_2CONR^6R^7$ ;  $R^2$  is  $NHR^{12}$  where  $R^{12}$  represents a phenyl group optionally substituted by one or more substituents selected from  $C_{1-6}$ alkyl, halo, hydroxy,  $C_{1-4}$ alkoxy,  $(CH_2)_q$ -tetrazolyl optionally substituted in the tetrazole ring by  $C_{1-4}$ alkyl,  $(CH_2)_q$ -imidazolyl,  $(CH_2)_q$ -triazolyl, 5-hydroxy-4-pyrone,  $NR^6R^7$ ,  $NR^9COR^{11}$ ,  $NR^9CONR^9R^{11}$ ,  $CONR^6R^7$ ,  $SO(C_{1-6}alkyl)$ ,  $SO_2(C_{1-6}alkyl)$ , trifluoromethyl,  $CONHSO_2R^8$ ,  $SO_2NHCOR^8$ ,  $SO_2NHR^{10}$ ,  $B(OH)_2$  and  $(CH_2)_qCO_2H$ ; or  $R^{12}$  represents a group

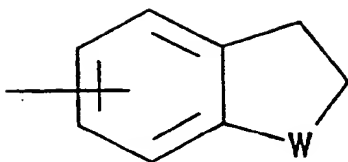


and  $R^4$  and  $R^5$  together form the residue of a bridged azabicyclic ring system.

5. A compound as claimed in claim 4 wherein  $R^1$  represents  $C_{1-6}$ alkyl,  $C_{3-7}$ cycloalkyl, cyclopropylmethyl,  $CH_2CO_2R^{11}$  or  $CH_2CONR^6R^7$ ; and  $R^{12}$  represents a phenyl group optionally substituted by one or more substituents selected from  $C_{1-6}$ alkyl, halo, hydroxy,  $C_{1-4}$ alkoxy,  $(CH_2)_q$ -tetrazolyl optionally substituted in the tetrazole ring by  $C_{1-4}$ alkyl,  $(CH_2)_q$ -imidazolyl,  $(CH_2)_q$ -triazolyl, 5-hydroxy-4-pyrone,  $NR^6R^7$ ,  $NR^9COR^{11}$ ,  $NR^9CONR^9R^{11}$ ,  $CONR^6R^7$ ,  $SO(C_{1-6}alkyl)$ ,  $SO_2(C_{1-6}alkyl)$ , trifluoromethyl,  $CONHSO_2R^8$ ,  $SO_2NHCOR^8$ ,  $SO_2NHR^{10}$ ,  $B(OH)_2$  and  $(CH_2)_tCO_2H$ , where  $t$  is zero, 1 or 2; or

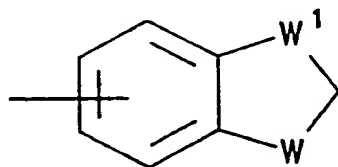
$R^{12}$  represents a group

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where W represents  $\text{CH}_2$  or  $\text{NR}^9$ .

6. A compound as claimed in claim 1 wherein  $\text{R}^1$  represents H,  $\text{C}_1$ -6alkyl,  $\text{C}_3$ -7cycloalkyl, cyclopropylmethyl,  $\text{CH}_2\text{CO}_2\text{R}^{11}$  or  $\text{CH}_2\text{CONR}^6\text{R}^7$ ;  $\text{R}^{12}$  represents a phenyl group optionally substituted by one or more substituents selected from  $\text{C}_1$ -6alkyl, halo, hydroxy,  $\text{C}_1$ -4alkoxy,  $(\text{CH}_2)_q$ -tetrazolyl optionally substituted in the tetrazole ring by  $\text{C}_1$ -4alkyl,  $(\text{CH}_2)_q$ -imidazolyl,  $(\text{CH}_2)_q$ -triazolyl, 5-hydroxy-4-pyrone,  $\text{NR}^6\text{R}^7$ ,  $\text{NR}^9\text{COR}^{11}$ ,  $\text{NR}^9\text{CONR}^9\text{R}^{11}$ ,  $\text{CONR}^6\text{R}^7$ ,  $\text{SO}(\text{C}_1$ -6alkyl),  $\text{SO}_2(\text{C}_1$ -6alkyl), trifluoromethyl,  $\text{CONHSO}_2\text{R}^8$ ,  $\text{SO}_2\text{NHCOR}^8$ ,  $\text{SO}_2\text{NHR}^{10}$ ,  $\text{B}(\text{OH})_2$  and  $(\text{CH}_2)_q\text{CO}_2\text{H}$ ; or  $\text{R}^{12}$  represents a group



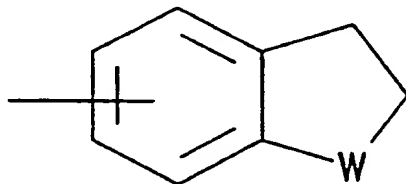
- and  $\text{R}^4$  and  $\text{R}^5$  are independently selected from H,  $\text{C}_1$ -12alkyl,  $\text{C}_4$ -9cycloalkyl $(\text{CH}_2)_k$  optionally substituted by one or more  $\text{C}_1$ -4alkyl groups, bridged  $\text{C}_6$ -10bicycloalkyl,  $(\text{CH}_2)_k\text{R}^{20}$  (where  $\text{R}^{20}$  is  $\text{NR}^6\text{R}^7$  as previously defined, or an azacyclic or azabicyclic group and k is 0, 1, 2, 3 or 4), optionally substituted aryl, and optionally substituted aryl $\text{C}_1$ -6alkyl.

7. A compound as claimed in claim 6 wherein  $\text{R}^1$  represents  $\text{C}_1$ -6alkyl,  $\text{C}_3$ -7cycloalkyl,

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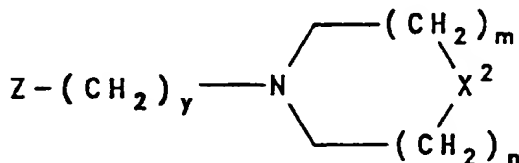
cyclopropylmethyl,  $\text{CH}_2\text{CO}_2\text{R}^{11}$  or  $\text{CH}_2\text{CONR}^6\text{R}^7$ ; and  $\text{R}^{12}$  represents a phenyl group optionally substituted by one or more substituents selected from  $\text{C}_{1-6}$ alkyl, halo, hydroxy,  $\text{C}_{1-4}$ alkoxy,  $(\text{CH}_2)_q$ -tetrazolyl optionally substituted in the tetrazole ring by  $\text{C}_{1-4}$ alkyl,  $(\text{CH}_2)_q$ -imidazolyl,  $(\text{CH}_2)_q$ -triazolyl, 5-hydroxy-4-pyrone,  $\text{NR}^6\text{R}^7$ ,  $\text{NR}^9\text{COR}^{11}$ ,  $\text{NR}^9\text{COR}^9\text{R}^{11}$ ,  $\text{CONR}^6\text{R}^7$ ,  $\text{SO}(\text{C}_{1-6}\text{alkyl})$ ,  $\text{SO}_2(\text{C}_{1-6}\text{alkyl})$ , trifluoromethyl,  $\text{CONHSO}_2\text{R}^8$ ,  $\text{SO}_2\text{NHCOR}^8$ ,  $\text{SO}_2\text{NHR}^{10}$ ,  $\text{B}(\text{OH})_2$  and  $(\text{CH}_2)_t\text{CO}_2\text{H}$ , where  $t$  is zero, 1 or 2;

or

 $\text{R}^{12}$  represents a group

where  $\text{W}$  represents  $\text{CH}_2$  or  $\text{NR}^9$ ; and  $\text{R}^4$  and  $\text{R}^5$  are independently selected from  $\text{H}$ ,  $\text{C}_{1-12}$ alkyl,  $\text{C}_{4-9}$ cycloalkyl, optionally substituted aryl, optionally substituted aryl $\text{C}_{1-6}$ alkyl, and azacyclic and azabicyclic groups.

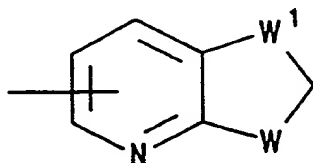
8. A compound as claimed in claim 1 wherein  $\text{R}^1$  represents  $\text{C}_{1-6}$ alkyl,  $\text{C}_{3-7}$ cycloalkyl, cyclopropylmethyl,  $\text{CH}_2\text{CO}_2\text{R}^{11}$  or  $\text{CH}_2\text{CONR}^6\text{R}^7$ ;  $\text{R}^2$  represents  $\text{NHR}^{12}$  where  $\text{R}^{12}$  represents phenyl substituted by a group



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and  $R^4$  and  $R^5$  each independently represents H,  
 $C_{1-12}$ alkyl,  $C_{4-9}$ cycloalkyl, optionally substituted aryl,  
 optionally substituted aryl $C_{1-6}$ alkyl or an azacyclic or  
 azabicyclic group, or  $R^4$  and  $R^5$  together form the residue  
 5 of an azacyclic or a bridged azabicyclic ring system.

9. A compound as claimed in claim 1 wherein  
 $R^1$  represents H,  $C_{1-6}$ alkyl,  $C_{3-7}$ cycloalkyl,  
 cyclopropylmethyl,  $(CH_2)_r$ imidazolyl,  $(CH_2)_r$ triazolyl,  
 10  $(CH_2)_r$ tetrazolyl,  $CH_2CO_2R^{11}$  or  $CH_2CONR^6R^7$ ;  $R^2$  represents  
 $NHR^{12}$  where  $R^{12}$  represents a pyridyl group optionally  
 substituted by one or more substituents selected from  
 $C_{1-6}$ alkyl, halo, hydroxy,  $C_{1-4}$ alkoxy,  $(CH_2)_q$ -tetrazolyl  
 optionally substituted in the tetrazole ring by  
 15  $C_{1-4}$ alkyl,  $(CH_2)_q$ -imidazolyl,  $(CH_2)_q$ -triazolyl, 5-  
 hydroxy-4-pyrone,  $NR^6R^7$ ,  $NR^9COR^{11}$ ,  $NR^9CONR^{9'}R^{11}$ ,  $CONR^6R^7$ ,  
 $SO(C_{1-6}alkyl)$ ,  $SO_2(C_{1-6}alkyl)$ , trifluoromethyl,  
 $CONHSO_2R^8$ ,  $SO_2NHCOR^8$ ,  $SO_2NHR^{10}$ ,  $B(OH)_2$  and  $(CH_2)_qCO_2H$ ; or  
 $R^{12}$  represents a group

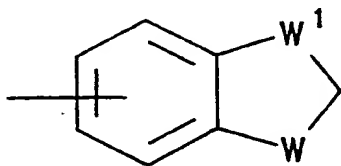


25 and  $R^4$  and  $R^5$  each independently represents H,  
 $C_{1-12}$ alkyl,  $C_{4-9}$ cycloalkyl optionally substituted by one  
 or more  $C_{1-4}$ alkyl groups,  $C_{4-9}$ cycloalkyl $C_{1-4}$ alkyl,  
 optionally substituted aryl, optionally substituted  
 aryl $C_{1-6}$ alkyl or an azacyclic or azabicyclic group, or  $R^4$   
 30 and  $R^5$  together form the residue of an optionally  
 substituted azacyclic or a bridged azabicyclic ring  
 system.

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10. A compound as claimed in claim 1 wherein  $R^1$  represents H,  $C_{1-6}$ alkyl,  $C_{3-7}$ cycloalkyl, cyclopropylmethyl,  $(CH_2)_r$ imidazolyl,  $(CH_2)_r$ triazolyl,  $(CH_2)_r$ tetrazolyl,  $CH_2CO_2R^{11}$  or  $CH_2CONR^6R^7$ ;  $R^2$  represents  $(CH_2)_sR^{13}$ ; and  $R^4$  and  $R^5$  together form the residue of an azacyclic or azabicyclic ring system.

11. A compound as claimed in claim 1 wherein  $R^1$  represents H,  $C_{1-6}$ alkyl,  $C_{3-7}$ cycloalkyl, cyclopropylmethyl,  $(CH_2)_r$ imidazolyl,  $(CH_2)_r$ triazolyl,  $(CH_2)_r$ tetrazolyl,  $CH_2CO_2R^{11}$  or  $CH_2CONR^6R^7$ ;  $R^2$  is  $NHR^{12}$  where  $R^{12}$  represents a phenyl group optionally substituted by one or more substituents selected from  $C_{1-6}$ alkyl, halo, hydroxy,  $C_{1-4}$ alkoxy,  $(CH_2)_q$ -tetrazolyl optionally substituted in the tetrazole ring by  $C_{1-4}$ alkyl,  $(CH_2)_q$ -imidazolyl,  $(CH_2)_q$ -triazolyl, 5-hydroxy-4-pyrone,  $NR^6R^7$ ,  $NR^9COR^{11}$ ,  $NR^9CONR^9R^{11}$ ,  $CONR^6R^7$ ,  $SO(C_{1-6}alkyl)$ ,  $SO_2(C_{1-6}alkyl)$ , trifluoromethyl,  $CONHSO_2R^8$ ,  $SO_2NHCOR^8$ ,  $SO_2NHR^{10}$ ,  $B(OH)_2$  and  $(CH_2)_qCO_2H$ ; or  $R^{12}$  represents a group



and  $R^4$  and  $R^5$  together form the residue of a fused or spiro azabicyclic ring system.

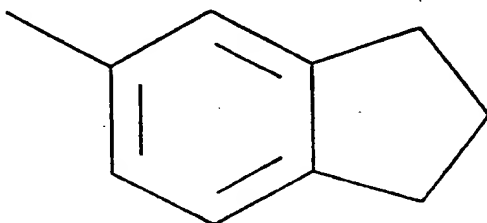
12. A compound as claimed in any preceeding claim wherein  $R^1$  is  $C_{1-6}$ alkyl.

13. A compound as claimed in claim 1 wherein  $R^1$  is  $C_{1-6}$ alkyl substituted by one or more halo.



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14. A compound as claimed in claim 1, claim 12 or claim 13 wherein  $R^2$  represents  $NHR^{12}$  and  $R^{12}$  represents phenyl substituted by one or two substituents selected from  $C_{1-6}$ alkyl, halo and trifloromethyl; or  $R^{12}$  represents



15. A compound as claimed in claim 1, claim 12, claim 13 or claim 14 wherein  $R^4$  and  $R^5$  together form the residue of an azacyclic ring system substituted by one or more methyl groups, or  $R^4$  and  $R^5$  together form the residue of a bridged azabicyclic ring system.

16. A compound as claimed in claim 1 selected from:

N-[3(R,S)-2,3-dihydro-5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl]-N'-[3-methylphenyl]urea;

N-[3(R,S)-2,3-dihydro-2-oxo-5-(4-oxopiperidin-1-yl)-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

N-[3(R,S)-2,3-dihydro-2-oxo-1-propyl-5-(4-[1,1,1-trifluoroethylamine]piperidin-1-yl)-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

N-[3(R,S)-2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[indan-5-yl]urea;

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- (-)-N-[2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[indan-5-yl]urea;
- 5 (+)-N-[2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[indan-5-yl]urea;
- N-[3(R,S)-2,3-dihydro-5-(cis-2,6-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;
- 10 N-[3(R,S)-2,3-dihydro-1-methyl-5-(4-methylpiperidin-1-yl)-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;
- (+)-N-[2,3-dihydro-1-methyl-5-(4-methylpiperidin-1-yl)-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;
- 15 (-)-N-[2,3-dihydro-1-methyl-5-(4-methylpiperidin-1-yl)-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;
- N-[3(R,S)-2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;
- 20 (+)-N-[2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;
- (-)-N-[2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;
- 25 N-[3(R,S)-2,3-dihydro-5-(4-methoxypiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;
- (-)-N-[2,3-dihydro-1-methyl-5-(4-methylpiperidin-1-yl)-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[indan-5-yl]urea;
- 30 N-[3(R,S)-2,3-dihydro-5-(cis-2,6-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[indan-5-yl]urea;

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(+)-N-[2,3-dihydro-5-(4-methoxypiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

(-)-N-[2,3-dihydro-5-(4-methoxypiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

5 (+)-N-[2,3-dihydro-5-(cis-2,6-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[indan-5-yl]urea;

(-)-N-[2,3-dihydro-5-(cis-2,6-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[indan-5-yl]urea;

10 N-[3(R,S)-2,3-dihydro-5-(cis-2,6-dimethylmorpholin-4-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

15 N-[3(R,S)-2,3-dihydro-5-(4-methylpiperidin-1-yl)-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

(+)-N-[2,3-dihydro-5-(4-methylpiperidin-1-yl)-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

20 (-)-N-[2,3-dihydro-5-(4-methylpiperidin-1-yl)-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

N-[3(R,S)-2,3-dihydro-1-methyl-2-oxo-5-(4-trifluoromethylpiperidin-1-yl)-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

25 (+)-N-[2,3-dihydro-1-methyl-2-oxo-5-(4-trifluoromethylpiperidin-1-yl)-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

(-)-N-[2,3-dihydro-1-methyl-2-oxo-5-(4-trifluoromethylpiperidin-1-yl)-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

30 N-[3(R,S)-2,3-dihydro-5-(2,2-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

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(+)-N-[2,3-dihydro-5-(2,2-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

5 (-)-N-[2,3-dihydro-5-(2,2-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

N-[3(R,S)-2,3-dihydro-1-methyl-2-oxo-5-(cis-2,4,6-trimethylpiperidin-1-yl)-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

10 (+)-N-[2,3-dihydro-1-methyl-2-oxo-5-(cis-2,4,6-trimethylpiperidin-1-yl)-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

15 (-)-N-[2,3-dihydro-1-methyl-2-oxo-5-(cis-2,4,6-trimethylpiperidin-1-yl)-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

N-[3(R,S)-2,3-dihydro-5-(3,3-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

20 (+)-N-[2,3-dihydro-5-(3,3-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

(-)-N-[2,3-dihydro-5-(3,3-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

25 N-[3(R,S)-2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-2-oxo-1-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

30 (+)-N-[2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-2-oxo-1-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

(-)-N-[2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-2-oxo-1-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

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- N-[3(R,S)-2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-ethyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;  
(-)-N-[2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-ethyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;  
5 N-[3(R,S)-5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;  
10 N-[3(R,S)-2,3-dihydro-5-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;  
(-)-N-[5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;  
15 (+)-N-[5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;  
N-[3(R,S)-5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-fluorophenyl]urea;  
20 (-)-N-[5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-fluorophenyl]urea;  
25 (+)-N-[5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-fluorophenyl]urea;  
N-[3(R,S)-5-(3-azabicyclo[3.2.1]octan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;  
30 (-)-N-[5-(3-azabicyclo[3.2.1]octan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

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(+)-N-[5-(3-azabicyclo[3.2.1]octan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-(3-methylphenyl)urea;

5 (-)-N-[5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-(5-indanyl)urea;

N-[3(R,S)-5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-(3-trifluoromethylphenyl)urea;

10 N-[3(R,S)-2,3-dihydro-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl] N'-(3-methylphenyl)urea;  
N-[3(R,S)-5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-(3-fluoro-4-methylphenyl)urea;

15 (-)-N-[5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-(3-fluoro-4-methylphenyl)urea;

(+)-N-[5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-(3-fluoro-4-methylphenyl)urea;

20 N-[3(R,S)-5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-(3-iodophenyl)urea;

25 (-)-N-[5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-(3-iodophenyl)urea;

(+)-N-[5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-(3-iodophenyl)urea;

30

N-[3(R,S)-5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[phenyl]urea;

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N-[3(R,S)-5-(2-azabicyclo[2.2.2]octan-2-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

5 N-[3(R,S)-5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[4-fluoro-3-methylphenyl]urea;

(-)-N-[5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[4-fluoro-3-methylphenyl]urea;

10 (+)-N-[5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[4-fluoro-3-methylphenyl]urea;

(-)-N-[5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-

15 trifluoromethylphenyl]urea;

(+)-N-[5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-trifluoromethylphenyl]urea;

20 N-[3(R,S)-2,3-dihydro-1-methyl-5-(cis-octahydroisoindol-2-yl)-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

(-)-N-[2,3-dihydro-1-methyl-5-(cis-octahydroisoindol-2-yl)-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

25 (+)-N-[2,3-dihydro-1-methyl-5-(cis-octahydroisoindol-2-yl)-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

N-[3(R,S)-5-(N-cyclohexyl-N-methylamino)-2,3-dihydro-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl] N'-[3-

30 methylphenyl]urea;

(-)-5-(N-cyclohexyl-N-methylamino)-2,3-dihydro-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl N'-[3-methylphenyl]urea;

(+)-5-(N-cyclohexyl-N-methylamino)-2,3-dihydro-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl N'-[3-methylphenyl]urea;

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N-[3(R,S)-5-(N-cyclohexyl-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

5 (-)-5-(N-cyclohexyl-N-methylamino)-2,3-dihydro-2-oxo-1-methyl-1H-1,4-benzodiazepin-3-yl N'-[3-methylphenyl]urea;

(+)-5-(N-cyclohexyl-N-methylamino)-2,3-dihydro-2-oxo-1-methyl-1H-1,4-benzodiazepin-3-yl N'-[3-methylphenyl]urea;

10 N-[3(R,S)-5-(N-cycloheptyl-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

(-)-5-(N-cycloheptyl-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl N'-[3-methylphenyl]urea;

(+)-5-(N-cycloheptyl-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl N'-[3-methylphenyl]urea;

15 N-[3(R,S)-5-(N-cycloheptyl-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[5-indanyl]urea;

(-)-5-(N-cycloheptyl-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl N'-[5-indanyl]urea;

20 (+)-5-(N-cycloheptyl-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl N'-[5-indanyl]urea;

N-[3(R,S)-5-(N-benzyl-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

25 N-[3(R,S)-5-(N-(4-N-methylpiperidiny)-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

N-[3(R,S)-5-(N-cyclohexylmethyl-N-methylamino)-2,3-dihydro-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

30 N[3(R,S)-5-(N,N-di-n-propylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;



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N-[3(R,S)-5-(N-(N-cyclopentyl-N-ethylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

5 N-[3(R,S)-5-(N-(4,4-dimethylcyclohexyl)-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

N-[3(R,S)-5-(N-cyclohexyl-N-ethylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

10 N-[3(R,S)-5-(N-cyclohexyl-N-propylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

N-[3(R,S)-5-(N-benzyl-N-cyclohexylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

15 N-[3(R,S)-5-(N-cyclohexylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

N-[3(R,S)-5-(N-cyclohexyl-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[5-indanyl]urea;

20 N-[3(R,S)-5-(N-cyclooctyl-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

N-[3(R,S)-2,3-dihydro-5-(2-(N,N-dimethylamino)ethylamino)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

25 N-[3(R,S)-2,3-dihydro-5-(N-(2-N-morpholinoethyl)-N-methylamino)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-methylphenyl]urea;

30 N-[3(R,S)-5-((N-cycloheptyl)-N-methylamino)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-(5-methylpyridine)]urea;

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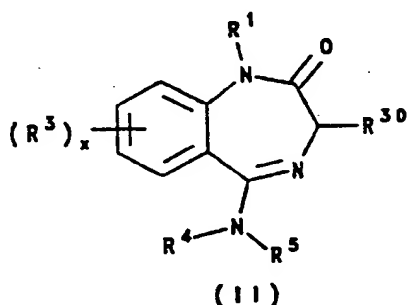
- 3(R,S)-N-(5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide;  
(-)-N-(5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide;  
5 (+)-N-(5-(3-azabicyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide;  
10 3(R,S)-N-(2,3-dihydro-5-(homopiperidin-1-yl)-1-(2-methylpropyl)-2-oxo-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide;  
(-)-N-(2,3-dihydro-5-(homopiperidin-1-yl)-1-(2-methylpropyl)-2-oxo-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide;  
15 (+)-N-(2,3-dihydro-5-(homopiperidin-1-yl)-1-(2-methylpropyl)-2-oxo-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide;  
3(R,S)-N-(2,3-dihydro-5-(homopiperidin-1-yl)-1-(2-methylpropyl)-2-oxo-1H-1,4-benzodiazepin-3-yl)-(2S)-indoline-2-carboxamide;  
20 3(R,S)-N-(2,3-dihydro-5-(homopiperidin-1-yl)-1-(2-methylpropyl)-2-oxo-1H-1,4-benzodiazepin-3-yl)-1H-indole-3-acetamide;  
25 3(R,S)-N-(2,3-dihydro-5-(4-methylpiperidin-1-yl)-1-(2-methylpropyl)-2-oxo-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide;  
N-[3(R,S)-2,3-dihydro-1-methyl-5-(4-methylpiperidin-1-yl)-2-oxo-1H-1,4-benzodiazepin-3-yl] N'-[3-(N-methyl-N'-piperazinyl)phenyl]urea;  
30 and salts and prodrugs thereof.

17. A compound as claimed in any preceding claim for use in therapy.

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18. A process for the preparation of a compound as claimed in claim 1, which process comprises:

- (A) reacting an intermediate of formula (II)  
 5 with a compound of formula (III)



(III)

wherein  $R^1$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^{12}$  and  $x$  are as defined for formula (I), one of  $R^{30}$  and  $R^{31}$  represents  $NH_2$  and the other of  $R^{30}$  and  $R^{31}$  represents  $-N=C=O$ ; or

- (B) reacting an intermediate of formula (II)  
 20 wherein  $R^{30}$  is  $NH_2$  with a compound of formula  $HOC(=O)(CH_2)_sR^{13}$ , wherein  $R^{13}$  and  $s$  are as defined for formula (I), in the presence of a base and a coupling reagent;  
 and optionally converting the compound of formula (I)  
 25 obtained to a salt or prodrug thereof.

19. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 16 in association with a pharmaceutically acceptable carrier.

30

20. The use of a compound as claimed in any one of claims 1 to 16 for the manufacture of a medicament for the treatment of a physiological disorder involving CCK and/or gastrin.

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21. The use of a compound as claimed in any one of claims 1 to 16 for the manufacture of a medicament for the treatment of panic, anxiety or pain.

5

22. A process for preparing a composition as claimed in claim 19 which process comprises bringing a compound as claimed in any of claims 1 to 16 into association with a pharmaceutically acceptable carrier or excipient.

10

23. A method for the treatment or prevention of a physiological disorder involving CCK and/or gastrin, which method comprises administration to a patient in need thereof of a CCK and/or gastrin reducing amount of a compound according to claim 1.

15

24. A method as claimed in claim 23 for the treatment or prevention of anxiety.

20

25. A method as claimed in claim 23 for the treatment or prevention of panic.

26. A method as claimed in claim 23 for the treatment or prevention of pain.

25

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D243/14 A61K31/55 C07D401/04 C07D401/12 C07D401/14  
 C07D403/04 C07D403/14 C07D413/04 C07D453/06 C07D487/08  
 C07D491/10 //(C07D487/08, 209:00, 209:00), (C07D491/10, 317:00,

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 434 369 (MERCK AND CO.) 26 June 1991 see claims; examples 3,5-7,9,10,12 ---	1-26
A	EP,A,0 434 364 (MERCK AND CO.) 26 June 1991 see claims ---	1-26
A	JOURNAL OF MEDICINAL CHEMISTRY vol. 32, no. 1, January 1989, WASHINGTON US pages 13 - 16 M G BOCK ET AL 'Benzodiazepine gastrin and brain cholecystokin receptor ligands L-365260' cited in the application see the whole document ---	1-26

-/--

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*A\* document member of the same patent family

Date of the actual completion of the international search

22 November 1993

Date of mailing of the international search report

- 3. 12. 93

Name and mailing address of the ISA

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Authorized officer

HEYWOOD, C

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB93/01599

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 17,23-26 are directed to a method of treatment of the human animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
As the drafting of the claims is not concise (Art.6) and encompasses an enormous number of compounds not supported by the description, the search has been carried out, on economic grounds, on the basis of the claimed examples. (Guidelines for examin. in the EPO, Part. B, Chapt. III, 3.7)
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 93/01599

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0434369	26-06-91	CA-A- 2032226	19-06-91
EP-A-0434364	26-06-91	AU-A- 6815190	20-06-91
EP-A-0539170	28-04-93	AU-A- 2788792	21-05-93
		WO-A- 9308176	29-04-93

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